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(54) Title: NUCLEIC ACIDS, PROTEINS, AND ANTIBODIES

(57) Abstract:

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(71) **Applicant** (for all designated States except US): **HUMAN GENOME SCIENCES, INC.** [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).

(72) **Inventors; and**

(75) **Inventors/Applicants** (for US only): **ROSEN, Craig, A.** [US/US]; 22400 Rolling Hill Lane, Laytonsville, MD 20882 (US). **BARASH, Steven, C.** [US/US]; 111 Watkins Pond Blvd., #301, Rockville, MD 20850 (US). **RUBEN, Steven, M.** [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832 (US).

(74) **Agents:** **HOOVER, Kenley, K.** et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Nucleic Acids, Proteins, and Antibodies

[1] This application refers to a "Sequence Listing" that is provided only on electronic media in computer readable form pursuant to Administrative Instructions Section 801(a)(i). The Sequence Listing forms a part of this description pursuant to Rule 5.2 and Administrative Instructions Sections 801 to 806, and is hereby incorporated in its entirety.

[2] The Sequence Listing is provided as an electronic file (PJZ01_seqList.txt, 622,696 bytes in size, created on January 13, 2001) on four identical compact discs (CD-R), labeled "COPY 1," "COPY 2," "COPY 3," and "CRF." The Sequence Listing complies with Annex C of the Administrative Instructions, and may be viewed, for example, on an IBM-PC machine running the MS-Windows operating system by using the V viewer software, version 2000 (see World Wide Web URL: <http://www.fileviewer.com>).

Field of the Invention

[3] The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to

these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Background of the Invention

[4] Blood is composed of a fluid component, plasma, in which are suspended red and white blood cells and platelets. This suspension, circulating through the cardiovascular system, forms the basis of the immune system, provides all of the body's tissues with oxygen and nutrients, and removes carbon dioxide and other metabolic byproducts for excretion.

[5] Immune cells, red blood cells, and platelets, are derived from common precursor stem cells by a process known as hematopoiesis. During fetal life hematopoiesis occurs in the liver and spleen, but in the adult, hematopoiesis occurs mainly in bone marrow. The stem cells from which all blood cells are derived proliferate and differentiate into the various blood cell lineages, (e.g., lymphocytes (B or T cells), myeloid cells (basophils, eosinophils, neutrophils, mast cells, macrophages), platelets, or red blood cells) in response to signals received from other cells (e.g., stromal cells) in the bone marrow microenvironment and also from cytokines. Many of the cytokines that promote the growth and differentiation of hematopoietic stem cells are known as "colony stimulating factors". For example, interleukin-3 (IL-3, and also known as multi-colony stimulating factor) and granulocyte macrophage colony stimulating factor (GM-CSF), which are released by activated macrophages T cells, stimulate the production of macrophages and granulocytes (myelopoiesis). Stem cell factor (SCF, c-kit ligand) is a growth factor for primitive lymphoid and myeloid hematopoietic bone marrow progenitor cells expressing the early cell surface marker CD34. Other hematopoietic cytokines/growth factors include, but are not limited to macrophage colony stimulating factor (M-CSF) and granulocyte colony stimulating factor (G-CSF). Interleukins-1, 6, and 7 have also been shown to function as hematopoietic growth factors/cytokines. Deficiencies in the quantities of mature red and white blood cells, either as a result of insufficient production or excessive destruction, may result in anemias and/or immunodeficiencies.

[6] In addition to the cellular component of the blood, there are a remarkable variety of soluble blood-borne proteins that subserve important physiological functions. Descriptions of some of the functional classes of blood proteins, along with representative members of these classes, are given below.

Coagulation factors

[7] The formation of insoluble protein aggregates at the site of vascular injury or inflammation, termed coagulation, is the result of multiple interacting coagulation factors (Dahlback, B., *Lancet* 355:1627-32). This cascade of interdependent proteins (including Factors V, VIII, IX, X XI, XII) results in the production of the protease, thrombin. Thrombin converts blood-soluble fibrinogen into fibrin, which polymerizes into insoluble clots which are stabilized by the activity of Factor XIII. This process is balanced by the activity of coagulation inhibitors such as antithrombin III, heparin cofactor II, Protein C and Protein S. Imbalance between pro-clotting factors and coagulation inhibitors leads to potentially serious medical conditions, including improper wound healing and the bleeding disorders hemophilia A and B, as well as excessive clotting disorders such as thrombosis (e.g. cerebral, coronary, and placental), pulmonary embolus, stroke, and coronary artery disease. For a more extensive review see Triplett, D., *Clin Chem* 46:1260-9.

Immunoproteins

[8] Blood plasma contains a number of proteins which contribute to the immune response. Immunoglobulin antibodies are glycoproteins with similar structural domains, which bind to specific antigenic invaders and trigger other components of the immune system. The complement cascade, a network of about 20 interacting proteins, is activated by antigen-antibody complexes and results in the lysis of infected cells, as well as other important immune functions. Immunoproteins are important tools for the diagnosis and treatment of infection, cancer, and other disorders. For more detailed discussion of immunoproteins see Meri, J. and Jarva, H., *Vox Sang* 74 suppl. 2:291-302 and Chapter 23 of Molecular Biology of the Cell, 3rd Edition, edited by Alberts, B. et al.

Hormones

[9] The blood serves as a major vehicle for hormones and other secreted signaling molecules which act at a site distant to their release. A number of peptide hormones function as regulators of homeostatic processes. For example, parathyroid hormone and calcitonin oppositely regulate serum levels of calcium. Blood-borne peptide hormones which regulate carbohydrate metabolism include insulin, glucagon, and adrenocorticotropin hormone. Vasopressin, angiotensin, and bradykinin are hormones which modulate vasodilation and blood pressure. Follicle-stimulating hormone and leutinizing hormone play important roles in both male and female reproductive functions. Dysfunction of these hormones can lead to a wide spectrum of disorders, including osteoporosis, diabetes, psychiatric disorders, hypoglycemia, obesity, infertility, as well as hypo- and hypertension.

Cytokines

[10] Cytokines are a class of circulating proteins which act primarily as intercellular signaling molecules regulating hematopoiesis, angiogenesis, and immune system functions. One subgroup of cytokines, the hematopoietins, regulate hematopoietic stem cell differentiation to maintain the proper number and proportions of each blood cell type. For example, the production of erythrocytes is stimulated by the release of erythropoietin from the kidneys in response to decreased blood oxygen levels. Similarly, thrombopoietin stimulates the proliferation and differentiation of megakaryocytes, leading to increased platelet production. Another cytokine subgroup, the chemokines, are secreted by cells of the immune system, and act to coordinate the immune response to an invading antigen. This is a large and diverse class of proteins, and includes RANTES, eotaxin, lymphotactin, MIP-1, and the interleukins. Many of these polypeptides have uses in the diagnosis and treatment of immunological disorders and infection (Holladay, J. et al., *Med Ped Oncol Suppl* 2:2-9; Chapter 23, *Immunology*, edited by Elgert, K.).

Carrier Proteins

[11] A number of soluble proteins found in blood function as carriers of other molecules such as nutrients and waste products. Carrier proteins can also bind exogenously delivered drugs and influence pharmacokinetic properties such as serum half-life and tissue adsorption. Serum albumin, comprising about half of the protein found in blood plasma,

regulates osmotic pressure of blood, as well as binds many bioactive molecules. Transferrin is a blood carrier protein that regulates iron levels, while ceruloplasmin regulates copper levels.

[12] The discovery of new human blood-related polynucleotides, the polypeptides encoded by them, and antibodies that immunospecifically bind these polypeptides, satisfies a need in the art by providing new compositions which are useful in the diagnosis, treatment, prevention and/or prognosis of disorders of the blood and/or blood forming organs, such as, for example, hemophilia, anemia, leukemia, immunodeficiency disorders (including AIDS), cardiovascular disease, stroke, metabolic disorders, and infectious or parasitic diseases.

Summary of the Invention

[13] The present invention relates to novel proteins. More specifically, isolated nucleic acid molecules are provided encoding novel polypeptides. Novel polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human polynucleotides and/or polypeptides, and antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting or enhancing the production and function of the polypeptides of the present invention.

Detailed Description

Tables

[14] Table 1A summarizes some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:)) and contig nucleotide sequence identifier (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides

encoded thereby. The first column provides the gene number in the application for each clone identifier. The second column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence disclosed in Table 1A. The third column provides a unique contig identifier, "Contig ID:" for each of the contig sequences disclosed in Table 1A. The fourth column provides the sequence identifier, "SEQ ID NO:X", for each of the contig sequences disclosed in Table 1A. The fifth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineate the preferred open reading frame (ORF) that encodes the amino acid sequence shown in the sequence listing and referenced in Table 1A as SEQ ID NO:Y (column 6). Column 7 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4; 181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1A as "Predicted Epitopes". In particular embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1A. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. Column 8, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first number in column 8 (preceding the colon), represents the tissue/cell source identifier code corresponding to the key provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. For those identifier codes in which the first two letters are not "AR", the second number in column 8 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate,

onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ^{33}P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression. Column 9 provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIMTM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). If the putative chromosomal location of the Query overlaps with the chromosomal location of a Morbid Map entry, an OMIM identification number is disclosed in column 10 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5.

[15] Table 1B summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier,

"Clone ID NO:Z", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

[16] Table 2 summarizes homology and features of some of the polypeptides of the invention. The first column provides a unique clone identifier, "Clone ID NO:Z", corresponding to a cDNA clone disclosed in Table 1A. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1A and allowing for correlation with the information in Table 1A. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequence. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of the PFAM/NR hit having a significant match to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in columns five and six. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth and sixth columns. In specific embodiments polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by a polynucleotide in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

[17] Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to contig sequences disclosed in Table 1A. The second column provides the sequence identifier, "SEQ ID NO:X", for contig sequences disclosed in Table 1A. The third column provides the unique contig identifier, "Contig ID:", for contigs disclosed in Table 1A. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEQ ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the invention are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone).

[18] Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1A, column 8. Column 1 provides the tissue/cell source identifier code disclosed in Table 1A, Column 8. Columns 2-5 provide a description of the tissue or cell source. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease". The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

[19] Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 1A, column 10. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM, McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). Column 2 provides diseases associated with the cytologic band disclosed in Table 1A, column 9, as determined using the Morbid Map database.

[20] Table 6 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

[21] Table 7 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

[22] Table 8 provides a physical characterization of clones encompassed by the invention. The first column provides the unique clone identifier, "Clone ID NO:Z", for certain cDNA clones of the invention, as described in Table 1A. The second column provides the size of the cDNA insert contained in the corresponding cDNA clone.

Definitions

[23] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[24] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

[25] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof; a nucleic acid sequence contained in SEQ ID NO:X (as described in column 3 of Table 1A) or the complement thereof; a cDNA sequence contained in Clone ID NO:Z (as described in column 2 of Table 1A and contained within a library deposited with the ATCC); a nucleotide sequence encoding the polypeptide encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or a fragment or variant thereof; or a nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereof. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

[26] In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 2 of Table 1A, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID NO:Z). Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Furthermore, certain clones disclosed in this application have been deposited with the ATCC on October 5, 2000, having the ATCC designation numbers PTA 2574 and PTA 2575; and on January 5, 2001, having the depositor reference numbers TS-1, TS-2, AC-1, and AC-2. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 7 provides a list of the deposited cDNA libraries. One can use the Clone ID NO:Z to determine the library source by reference to Tables 6 and 7. Table 7 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone (Clone ID) isolated from that library begins with the same four characters, for example "HTWEP07". As

mentioned below, Table 1A correlates the Clone ID names with SEQ ID NO:X. Thus, starting with an SEQ ID NO:X, one can use Tables 1, 6 and 7 to determine the corresponding Clone ID, which library it came from and which ATCC deposit the library is contained in. Furthermore, it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[27] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[28] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID NO:Z (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of cDNA clones deposited with the ATCC, described herein), and/or the polynucleotide sequence delineated in column 6 of Table 1B or the complement thereof. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[29] Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4 ; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[30] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[31] Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[32] The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or

DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

[33] The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, *PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES*, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); *POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS*, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., *Meth. Enzymol.* 182:626-646 (1990); Rattan et al., *Ann. N.Y. Acad. Sci.* 663:48-62 (1992)).

[34] "SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables 1A or 2, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 6 of Table 1A. SEQ ID NO:X is identified by an integer specified in column 4 of Table 1A. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID NO:Z" refers to a cDNA clone described in column 2 of Table 1A.

[35] "A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[36] The polypeptides of the invention can be assayed for functional activity (e.g. biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Specifically, one of skill in the art may routinely assay blood and blood-forming organ associated polypeptides (including fragments and variants) of the invention for activity using assays as described in Examples 21, 22, 23, 24, 25, 29, 33 and 43.

[37] "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

[38] Table 1A summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and clones (Clone ID NO:Z) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby.

Polynucleotides and Polypeptides of the InventionTABLE 1A

Gene No:	Clone ID NO: Z	Config ID:	SEQ ID NO: X	ORF (From-To)	AA SEQ ID NO: Y	Predicted Epitopes	Tissue Distribution Library code: count (see Table IV for Library Codes)	Cytologic Band	OMIM Disease Reference(s):
1	HPLBY29	1041126	11	461 - 3	155	Arg-19 to Phe-27, Ala-41 to Arg-48, Pro-70 to Thr-76, Glu-80 to Leu-85, Asn-94 to Pro-104, Asn-120 to Ala-127.	AR061: 1, AR089: 0 H0030: 2, H0057: 1 and L0754: 1.		
		509875	85	461 - 3	229	Arg-19 to Phe-27, Ala-41 to Arg-48, Pro-70 to Thr-76, Glu-80 to Leu-85, Asn-94 to Pro-104, Asn-120 to Ala-127.			
		1102662	12	436 - 254	156				
2	HOUEU57	531182	86	45 - 182	230	Pro-1 to Glu-13, Arg-26 to Glu-31.	AR089: 2, AR061: 2 S0040: 1 and S0044: 1.		
		531182	86	45 - 182	230	Pro-1 to Glu-13, Arg-26 to Glu-31.			
		1151373	13	414 - 767	157	Glu-1 to Ile-8,			
3	HNHFR39						AR061: 7, AR089: 6		

4	HFATE17						Ser-49 to Ser-54.	S0053: 2, H0052: 1 and S0216: 1.		
		576399	87	201 - 308	231					
		1151475	14	483 - 268	158			AR061: 6, AR089: 2 L0749: 8, L0493: 2, L0605: 2, S0300: 1 and L0362: 1.		
5	HNGER43	662491	88	335 - 586	232		Pro-11 to Gly-20.			
		699391	15	97 - 204	159			AR061: 3, AR089: 2 S0052: 3		
6	HWAAE95	1135294	16	700 - 1269	160		Thr-16 to Gly-22, Pro-34 to Ser-46, Arg-79 to Gly-100, Gln-116 to Val-123, Leu-153 to Ser-161.	AR089: 9, AR061: 2 H0255: 1, H0318: 1, H0581: 1 and S0250: 1.		
		789051	89	3 - 224	233		Tyr-2 to Gly-10, Phe-23 to Arg-36.			
		638097	17	213 - 527	161		Ser-96 to Ala-102.	AR051: 35, AR054: 29, AR089: 24, AR050: 20, AR061: 7 S0002: 1, L0766: 1 and H0445: 1.		
7	HMSGL27	855759	90	318 - 127	234		Cys-8 to Gly-28, Pro-31 to Glu-36.			
		1161224	18	560 - 276	162		His-1 to Ser-6, Ala-74 to Thr-80.	AR089: 38, AR061: 10 L0750: 3, S0360: 2, H0441: 2, H0553: 2, L0776: 2, L0659: 2, L0744: 2, L0747: 2, H0542: 2, S0110: 1.		
8	HKIXB77									

9	HTNBM01	870018 1207944	91 19	165 - 443 3 - 1661	235 163	Asn-23 to Thr-28, Arg-120 to Leu-126, Thr-160 to Leu-167, Pro-195 to Val-204, His-206 to Gly-215, Phe-246 to Gly-251, Pro-267 to Gln-275, Thr-303 to Glu-311, Thr-373 to His-392. Gly-1 to Gln-8, Thr-36 to Glu-44.	S0400: 1, H0255: 1, H0645: 1, H0392: 1, H0333: 1, H0013: 1, H0156: 1, H0122: 1, H0052: 1, H0105: 1, H0014: 1, S0051: 1, H0687: 1, H0124: 1, H0135: 1, H0087: 1, H0264: 1, H0647: 1, L0631: 1, L0638: 1, L0641: 1, L0774: 1, L0775: 1, H0547: 1, H0539: 1, S0380: 1, S0332: 1, L0743: 1, L0749: 1, L0777: 1, S0192: 1 and H0506: 1.	
10	HBJGT92	910705 1193035	92 20	1 - 420 1864 - 1427	236 164	Gln-49 to Gln-54, Pro-69 to Thr-74,	AR050: 206, AR054: 89, AR051: 72, AR061: 2, AR089: 1 H0591: 1, T0067: 1, S0038: 1 and L0485: 1.	

11	HAGAT56						Glu-99 to Arg-105; Gln-108 to Asn-114.	and L0748: 1.			
		919507	93	275 - 490	237		Lys-7 to Ser-18, Pro-32 to Glu-51.				
		1218696	21	381 - 1097	165		Lys-35 to Asn-46.				
12	HCFMG57	924588	94	3 - 665	238		Lys-18 to Glu-30, Ile-33 to Glu-38, Asp-46 to Asp-55, Ser-67 to Glu-76, Glu-84 to Arg-94.	AR061: 2, AR089: 1 S0010: 2, S0430: 1, H0657: 1, S0222: 1, S0003: 1, H0040: 1, H0494: 1, S0126: 1, S0436: 1 and L0366: 1.			
		1205913	22	1837 - 1598	166		Glu-41 to Arg-47, Asp-72 to Asp-79.				
12	HCFMG57							AR089: 1, AR061: 0 H0218: 7, L0766: 5, L0761: 3, L0655: 3, H0547: 3, L0740: 3, H0656: 2, S0360: 2, H0486: 2, H0434: 2, H0553: 2, S0036: 2, H0135: 2, L0637: 2, L0805: 2, L0636: 2, L0664: 2, H0555: 2, L0439: 2, L0745: 2, L0747: 2, L0596: 2, L0581: 2, H0669: 1, H0663: 1, H0619: 1, H0369: 1, S0222: 1,			

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14	HMUBI13	933264	96	228 - 401	240	Ser-24 to Leu-33.	L0784: 1, L0659: 1, L0788: 1, L0664: 1, L0438: 1, H0648: 1, S0330: 1, L0602: 1, L0744: 1, L0748: 1, L0745: 1, L0747: 1, L0749: 1, L0752: 1, L0758: 1, L0608: 1, S0196: 1 and S0412: 1.		
		1189811	24	1032 - 271	168	Cys-35 to Val-41, Asn-52 to Asn-64, Gly-81 to Gly-88, Glu-117 to Gly-133, Arg-188 to Arg-194, Gly-200 to Gln-207, Pro-243 to His-250.	AR089: 17, AR061: 2 H0521: 5, L0759: 4, S0358: 3, L0757: 3, S0046: 2, H0494: 2, L0662: 2, L0740: 2, H0663: 1, H0638: 1, S0132: 1, H0549: 1, H0586: 1, H0590: 1, H0024: 1, H0083: 1, H0252: 1, H0591: 1, H0551: 1, H0059: 1, H0529: 1, L0389: 1, L0775: 1, L0776: 1, L0665: 1, L0438: 1, H0547: 1, H0435: 1, S0037: 1, L0439: 1, L0755: 1, S0434: 1, L0596: 1, L0604: 1, H0667: 1, H0543: 1 and H0422: 1.		

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23

17	HCWGE12	1171961	27	116 - 3	171			AR061: 1, AR089: 0 H0305: 3		
		967067	100	211 - 300	244					
18	HCEPY32	1199930	28	2 - 1132	172	Ala-1 to Asp-16, Lys-74 to Glu-84, Leu-87 to Val-94, Cys-134 to Val-139, Arg-154 to Tyr-190, Thr-208 to Asn-214, Asp-222 to Asp-229, Thr-234 to Pro-255, Pro-267 to Pro-277, Gln-292 to Gln-304, Ala-317 to Cys-323, Ser-355 to Asn-371.	AR061: 385, AR089: 280 L0766: 7, S0222: 2, H0052: 2, H0561: 2, L0774: 2, L0777: 2, H0156: 1, S0010: 1, H0264: 1, H0625: 1, L0761: 1, L0806: 1, L0776: 1, L0790: 1, L0793: 1, L0779: 1 and L0752: 1.			
		530520	101	2 - 376	245			AR089: 1, AR061: 1 H0309: 2		
19	HSVCH37	1081035	29	3 - 122	173					
		558195	102	3 - 122	246					
20	HOFNL18	1204713	30	1 - 768	174	Ser-24 to Gln-30, Gln-41 to Arg-51, Lys-56 to Lys-62, Glu-70 to Leu-75, Gln-93 to Lys-99, Arg-104 to Lys-110, Asp-120 to Asp-134, His-149 to Gly-170, Glu-200 to Ala-219, Glu-226 to Arg-237,	AR089: 9, AR061: 3 H0415: 1 and H0414: 1.			

21	HTOCCG37	666498	103	1 - 405			Glu-245 to Arg-252.	AR061: 11, AR089: 6 L0777: 4, L0766: 3, L0776: 3, L0439: 3, H0031: 2, L0809: 2, H0694: 2, L0591: 2, S6024: 1, H0656: 1, H0369: 1, H0051: 1, T0067: 1, H0272: 1, L0769: 1, L0805: 1, L0518: 1, L0519: 1, H0684: 1, L0779: 1, S0031: 1, L0584: 1 and L0366: 1.		
		1189012	31	117 - 863	247	175	Ser-26 to Pro-33. Pro-54 to Asn-65, Glu-116 to Cys-122, Pro-124 to Glu-131, Gln-170 to Gln-177, Asp-227 to Asp-236.			
22	HTEOF80	708888	104	3 - 218	248		Asn-7 to Thr-18, Glu-34 to Ser-39, His-59 to Asn-64.	AR061: 7, AR089: 3 H0616: 3		
		1143414	32	295 - 1047	176		Phe-1 to Ala-15, Gly-26 to Gly-32, Leu-35 to Pro-40, Gln-54 to Ser-71, Glu-87 to Asn-101, Tyr-135 to Gln-145, Tyr-177 to Val-182, Glu-212 to Phe-233, Cys-235 to Gly-245.			
22	HTEOF80	847224	105	2 - 262	249		Val-17 to Arg-23, Tyr-28 to Ser-34, Thr-41 to Cys-47.			

23	HSLDP32	1182295	33	404 - 3	177	Gln-88 to His-93, Gly-114 to Cys-133.	AR089: 1, AR061: 0 S0028: 2, H0135: 1, H0163: 1 and S0044: 1.			
24	HAICQ62	866241	106	12 - 257	250	Asn-6 to Lys-13.				
		1182256	34	63 - 581	178	Asp-1 to Gly-15, Glu-72 to Asp-77, Gly-113 to Val-118, Ala-126 to Thr-133, Leu-159 to Asn-164.	AR054: 9, AR050: 7, AR061: 6, AR089: 2, AR051: 1 S0132: 2, L0806: 2, S0328: 2, H0635: 1, H0316: 1 and H0494: 1.			
25	HRDBE43	888225	107	157 - 672	251	Asp-1 to Gly-15, Glu-72 to Asp-77, Gly-113 to Val-118, Ala-126 to Thr-133.				
		894862	35	2 - 1297	179	Gln-34 to Arg-40, Arg-65 to Asp-70, Pro-163 to Gly-173, Gly-220 to Asp-232, Tyr-260 to Ile-268, Gly-296 to Ser-304, Ser-334 to Arg-339, Arg-347 to Gly-352, Tyr-359 to Ser-366, Thr-391 to Met-396.	AR054: 17, AR061: 7, AR051: 4, AR089: 3, AR050: 2 L0776: 5, L0748: 5, L0794: 4, H0156: 2, H0616: 2, L0805: 2, L0777: 2, T0082: 1, H0124: 1, H0591: 1, H0561: 1, L0639: 1, L0637: 1, L0764: 1, L0655: 1, L0659: 1, L0517: 1, L0809: 1, L0790: 1, H0658: 1, L0747: 1, L0749: 1, L0758: 1 and L0759: 1.			

26	HSSKD85	947966 908141	108 36	1287 - 574 152 - 1081	252 180	Gly-30 to Arg-38, Gln-62 to Tyr-67, His-80 to Tyr-85, Tyr-96 to Gly-112, Glu-134 to Ser-141, Ser-160 to Cys-166, Thr-173 to Trp-179, Gln-212 to Asp-222, Gly-225 to Gly-231, Gly-269 to Asp-276, Asn-303 to Asn-310.	AR089: 5, AR061: 4 L0755: 8, H0013: 4, H0266: 4, L0747: 4, L0601: 4, S0026: 4, H0038: 2, S0144: 2, L0769: 2, L0774: 2, L0517: 2, L0789: 2, L0731: 2, L0758: 2, H0445: 2, S0116: 1, S0360: 1, H0580: 1, S0222: 1, H0635: 1, H0581: 1, H0545: 1, H0457: 1, S0250: 1, H0617: 1, H0124: 1, H0316: 1, H0135: 1, H0538: 1, L0761: 1, L0764: 1, L0766: 1, L0803: 1, L0804: 1, L0657: 1, L0659: 1, L0782: 1, L0383: 1, L0809: 1, L0368: 1, L0665: 1, H0519: 1, S0330: 1, S0028: 1, L0740: 1, L0749: 1, L0750: 1, L0777: 1, L0757: 1, L0591: 1, L0599: 1, S0194: 1 and S0276: 1.		
27	HCRMV17	1180333	37	495 - 1463	181	Glu-1 to Gly-7,	AR061: 1, AR089: 1		

28	HFOX77	1137799	38	1 - 363	253	910010	109	3 - 689	253	Gly-14 to Asp-34, Thr-61 to Leu-97, Leu-99 to Leu-106, Ile-112 to Lys-118, Glu-137 to Arg-154, Asp-182 to His-187, Thr-194 to Gln-200, Gly-210 to Leu-215, Met-243 to Glu-252, Ser-283 to Ser-306, Leu-313 to Gly-319. Tyr-28 to Leu-33, Ala-70 to Lys-87, Glu-106 to Gly-124, Gly-127 to Glu-160, Leu-179 to Asp-194.	L0602: 2, S0356: 1, S0250: 1, H0551: 1, L0761: 1 and S0436: 1.		
										Gly-1 to Gln-7, Ser-29 to Thr-34, Asn-60 to Cys-78, Gly-114 to Phe-120.	AR089: 10, AR061: 2 L0439: 7, L0438: 4, L0744: 4, L0596: 4, S0010: 3, L0776: 3, L0517: 3, L0731: 3, L0599: 3, H0677: 3, H0265: 2, H0556: 2, S0222: 2, H0031: 2, H0673: 2, H0169: 2, L0761: 2, L0659: 2, S0126: 2, L0748: 2, L0747: 2, L0591: 2, S0194: 2, S0276: 2, H0650: 1, H0341: 1,		

									H0255: 1, S0418: 1, L0005: 1, S0360: 1, S0046: 1, H0632: 1, L0622: 1, T0060: 1, H0122: 1, S0346: 1, H0581: 1, S0049: 1, H0024: 1, H0017: 1, H0071: 1, T0006: 1, L0142: 1, L0456: 1, S0036: 1, H0551: 1, S0386: 1, H0100: 1, H0494: 1, L0770: 1, L0769: 1, L0638: 1, L0772: 1, L0800: 1, L0766: 1, L0666: 1, L0664: 1, H0683: 1, H0660: 1, H0521: 1, S0027: 1, L0779: 1, L0777: 1, L0753: 1, L0755: 1, L0758: 1, H0445: 1 and H0667: 1.			
		910698	110	102 - 569	254	Gln-8 to Ala-13, Ser-46 to Thr-51, Asn-77 to Cys-95, Thr-112 to Gly-118.			AR054: 10, AR050: 2, AR061: 1, AR089: 1, AR051: 0 L0756: 5, S0222: 1, H0591: 1, T0067: 1,			
29	HBXCZ29	1226989	39	3 - 1658	183	Asn-22 to Thr-27, Arg-119 to Leu-125, Thr-159 to Leu-166, Pro-194 to Val-203, His-205 to Gly-214,						

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31

34	HLCMP75	937325	116	61 - 387	260	Arg-1 to Ala-10, Arg-61 to Gly-68, Ala-73 to Lys-82.	L0021: 1, S0049: 1, H0050: 1, H0328: 1, H0181: 1, H0063: 1, H0264: 1, H0625: 1, L0369: 1, L0371: 1, L0761: 1, L0772: 1, L0800: 1, L0662: 1, L0768: 1, L0364: 1, L0774: 1, L0523: 1, L0806: 1, L0653: 1, L0807: 1, L0809: 1, L0647: 1, L0664: 1, S0052: 1, S0216: 1, S0374: 1, H0670: 1, H0521: 1, H0522: 1, S0027: 1, L0742: 1, L0743: 1, L0745: 1, L0779: 1, L0755: 1, L0608: 1, H0423: 1 and H0506: 1.		
		1203728	44	121 - 1164	188	Glu-19 to Glu-30, Asp-86 to Glu-95, Pro-127 to Pro-145, Thr-204 to Trp-210, Ser-248 to Pro-257, Ser-259 to Ser-277, His-304 to Arg-310,	AR051: 1, AR050: 1, AR054: 1, AR061: 1, AR089: 1 H0545: 9, H0333: 4, L0754: 4, H0544: 3, H0546: 3, L0794: 3, L0743: 3, L0744: 3,		

35	HWHQR25	944722	117	2 - 946	261	Pro-341 to His-347.	L0757: 3, S0212: 2, S0360: 2, H0619: 2, H0124: 2, L0771: 2, L0521: 2, S0027: 2, L0751: 2, L0777: 2, L0605: 2, H0550: 1, L0623: 1, H0013: 1, H0150: 1, H0086: 1, H0123: 1, H0288: 1, H0553: 1, H0644: 1, H0628: 1, H0181: 1, H0163: 1, H0087: 1, H0100: 1, L0803: 1, L0655: 1, L0656: 1, L0659: 1, L0384: 1, L0809: 1, L0565: 1, H0547: 1, H0658: 1, S0037: 1, S0028: 1, S0206: 1, L0603: 1 and H0665: 1.		
		1126358	45	1 - 522	189	Ala-17 to Ala-27, Pro-30 to Cys-35, Pro-37 to His-46, Pro-53 to Glu-66, Asp-122 to Glu-131, Pro-163 to Gln-172. Pro-1 to Cys-10, Asn-14 to Thr-23, Cys-27 to Trp-33, Gln-40 to Asn-53,	AR054: 164, AR050: 143, AR051: 118, AR089: 1, AR061: 1 L0794: 5, L0777: 4,		

34

38	HPJEQ52	1216564	48	2 - 505	120	12 - 560	264	Gly-358 to Phe-364, Ser-387 to Pro-403, Gly-422 to Cys-434, Pro-436 to Asp-446, Pro-478 to Asp-484, Pro-497 to Arg-502, Pro-507 to Gly-513, Cys-520 to Cys-527, Met-545 to Arg-561, Lys-595 to Ala-601, Cys-649 to Gly-662, His-666 to Gln-671. Leu-45 to Lys-50, Gln-55 to Glu-74, Thr-114 to Ile-119.	AR089: 13, AR061: 6 S0007: 5, L0803: 3, S0126: 2, S0222: 1, H0581: 1, H0494: 1, L0800: 1, L0764: 1, H0520: 1 and S0152: 1.
39	HFIZB56	953155 1137798	121 49	2 - 559 2 - 799	121 49	2 - 559 2 - 799	265 193	Thr-23 to Ser-30, Arg-58 to Asp-64, Ala-75 to Asn-82, Glu-103 to Gln-112, Leu-119 to Thr-141, Lys-175 to Tyr-182, Asn-211 to Asn-218. Thr-23 to Ser-30,	AR089: 31, AR054: 28, AR050: 26, AR051: 24, AR061: 3 S0250: 1, H0030: 1, H0521: 1, S0192: 1 and S0242: 1.

40	HUKEPI8	1106982	50	1 - 588	194	Arg-58 to Asp-64, Ala-75 to Asn-82, Glu-103 to Gln-112, Leu-119 to Cys-126.	AR061: 14, AR054: 11, AR050: 9, AR089: 4 L0758: 2, H0059: 1, L0789: 1, L0665: 1, L0749: 1 and L0779: 1.			
41	HEEAN63	957456 1105522	123 51	852 - 265 220 - 930	267 195	Arg-53 to Asp-64, Pro-68 to Asp-76, Val-107 to Lys-112, Gln-128 to Val-137, Gln-150 to Tyr-167, Gly-197 to Arg-202, Ala-215 to Leu-221.	AR061: 1, AR089: 1 S0360: 1, H0261: 1, H0549: 1, H0550: 1, H0553: 1, H0038: 1, H0040: 1, L0803: 1, L0804: 1, L0775: 1, L0806: 1, L0809: 1, L0666: 1, H0519: 1, H0521: 1, L0750: 1, H0136: 1, H0543: 1 and H0352: 1.			
42	HTKAA03	960233 961002	124 52	183 - 722 2 - 202	268 196	Asn-1 to Thr-9, Thr-40 to Asp-51.	S0300: 1, S0028: 1 and T0047: 1.			
43	HTTKBI8	963346	53	2 - 2440	197	Thr-20 to Leu-32, Phe-102 to Lys-107, Ser-138 to Ile-146, Pro-179 to Asp-192, Gln-217 to Glu-232.	AR089: 14, AR061: 6 L0439: 9, L0740: 9, L0794: 8, L0747: 8, L0731: 8, L0744: 6, L0592: 6, L0599: 6.			

Ser-355 to Ser-361, Tyr-447 to Met-453, Gln-486 to Asp-503, Arg-516 to Gln-523, Ala-530 to Ile-542, Lys-561 to Cys-574, Asp-633 to Lys-639, Glu-660 to Leu-666, Leu-678 to Arg-685, Ser-696 to Glu-705, Ile-767 to Asn-773, Glu-775 to His-786, Arg-797 to Pro-806.	H0341: 5, S0222: 5, S0010: 5, H0038: 5, H0521: 5, S3014: 5, L0750: 5, L0752: 5, H0542: 5, H0170: 4, H0040: 4, H0056: 4, L0659: 4, L0748: 4, L0756: 4, L0608: 4, H0638: 3, H0580: 3, H0156: 3, H0024: 3, H0494: 3, L0766: 3, L0649: 3, L0805: 3, L0809: 3, L0665: 3, H0144: 3, H0672: 3, L0757: 3, L0758: 3, L0759: 3, H0624: 2, S0134: 2, L0415: 2, S0360: 2, H0329: 2, S0046: 2, H0575: 2, H0036: 2, L0471: 2, H0266: 2, S0003: 2, H0090: 2, H0551: 2, H0264: 2, H0412: 2, S0150: 2, L0774: 2, L0775: 2, L0375: 2, L0655: 2, L0519: 2, L0666: 2, L0664: 2, L0565: 2, L0438: 2, H0520: 2, H0547: 2, H0660: 2, S0044: 2,
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				H0555: 2, S0027: 2, S0206: 2, L0754: 2, L0777: 2, H0445: 2, L0589: 2, H0423: 2, H0556: 1, S0040: 1, S0114: 1, T0049: 1, H0656: 1, S0116: 1, S0212: 1, H0664: 1, S0420: 1, S0354: 1, S0358: 1, S0045: 1, S0132: 1, H0619: 1, S6026: 1, S0278: 1, H0369: 1, H0392: 1, H0438: 1, H0643: 1, S0346: 1, H0318: 1, H0310: 1, H0309: 1, H0263: 1, T0110: 1, H0439: 1, H0041: 1, H0562: 1, H0123: 1, H0050: 1, H0373: 1, T0010: 1, S6028: 1, S0214: 1, H0428: 1, H0622: 1, H0031: 1, H0644: 1, H0166: 1, H0674: 1, S0364: 1, H0634: 1, H0616: 1, T0067: 1, H0477: 1, H0623: 1, T0069: 1, S0112: 1, L0564: 1, T0041: 1, H0429: 1.			
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44	HPTZB93	1222478	54	243 - 935	198	Glu-1 to Lys-8, Asn-32 to Arg-43.	H0560: 1, H0625: 1, S0294: 1, S0450: 1, S0142: 1, S0422: 1, S0002: 1, H0695: 1, H0026: 1, L0763: 1, L0772: 1, L0643: 1, L0764: 1, L0768: 1, L0387: 1, L0381: 1, L0803: 1, L0806: 1, L0654: 1, L0606: 1, L0526: 1, L0529: 1, L0647: 1, L0789: 1, H0698: 1, L0352: 1, H0519: 1, H0690: 1, H0435: 1, H0648: 1, S0378: 1, S0152: 1, H0522: 1, H0696: 1, S0146: 1, H0626: 1, S0037: 1, L0753: 1, H0444: 1, L0480: 1, H0667: 1, S0192: 1, H0543: 1, S0042: 1, S0424: 1 and H0506: 1. AR089: 61, AR061: 22, AR051: 14, AR050: 2, AR054: 0 L0776: 5, L0789: 5, L0769: 3, L0805: 3, H0231: 1, H0213: 1, H0418: 1, L0794: 1,		
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45	HTSHM38	971842	125	850 - 164	269	Phe-28 to Arg-33, Pro-46 to Trp-51, Pro-54 to Pro-61, Arg-99 to Trp-108, Pro-174 to Gly-186, Glu-213 to Ala-225, Pro-230 to Arg-242. Asn-6 to Ser-15, Pro-29 to Arg-42, Pro-91 to Gln-108, Lys-123 to Arg-133, Ile-157 to Phe-168, Gln-171 to Val-178, Gly-185 to Pro-197.	L0750: 1 and L0731: 1. AR051: 26, AR054: 20, AR050: 18, AR089: 6, AR061: 2 H0087: 1 and H0264: 1.		
		1138085	55	432 - 1157	199				
		972248	126	2 - 604	270				
46	HELDY60	1056195	56	3 - 2633	200	Pro-10 to Arg-25, Arg-27 to Phe-36, Tyr-40 to Thr-46, Val-50 to Ile-58, Gly-77 to Ser-87, Pro-89 to Asn-118, Ser-120 to Trp-125, Thr-127 to Gly-156, Pro-158 to Met-169, Asp-173 to Trp-179, Gly-190 to Asp-201, Pro-211 to Gln-218, Pro-228 to Arg-235, Asp-258 to Asp-263,	AR051: 10, AR054: 8, AR061: 3, AR089: 2 H0170: 2, H0031: 2, L0748: 2, H0624: 1, S0360: 1, S0045: 1, H0013: 1, H0046: 1, H0068: 1, H0038: 1, L0662: 1, L0805: 1, L0776: 1, H0519: 1, H0696: 1 and L0731: 1.		

47	HNALE30	1219068	57	23 - 1852	201	Asp-182 to Trp-188. Pro-6 to Ser-17, Pro-30 to Ser-35, Ser-47 to Ser-57, Thr-63 to Ile-70, Lys-80 to Lys-88, Thr-108 to Ser-117, Pro-129 to Glu-134, Gln-164 to Ser-175, Val-273 to Leu-281.	AR089: 3, AR061: 1 H0135: 2, H0144: 2, L0439: 2, L0752: 2, H0619: 1, H0550: 1, H0083: 1, H0288: 1, H0040: 1, H0063: 1, H0380: 1, L0519: 1, L0438: 1, H0684: 1, S0027: 1, S0206: 1, L0743: 1, L0748: 1, L0754: 1 and H0543: 1.		
48	HWADY16	1182316	58	306 - 1007	202	Leu-1 to Lys-11, Thr-31 to Ser-40. Pro-1 to Pro-15, Tyr-51 to Asp-56, Asp-78 to Asn-88, Ala-101 to Glu-106, Gly-112 to Glu-117, Ala-153 to Arg-161, Glu-166 to Ser-176, Lys-192 to Ala-224, Arg-226 to Arg-234.	AR089: 1, AR061: 0 L0800: 2, L0766: 2, L0777: 2, H0581: 1, H0553: 1, L0771: 1, L0803: 1, L0774: 1, L0792: 1, H0522: 1, L0740: 1, L0755: 1, L0731: 1 and H0543: 1.		
49	HNTRU73	1173875	59	3 - 530	203	Pro-2 to Gly-9. Ala-35 to Lys-52, Glu-58 to Glu-84, Leu-103 to Asp-118, Thr-145 to Arg-176.	AR089: 2, AR061: 1 H0547: 1		
		910009	131	3 - 1190	275	Ala-35 to Lys-52, Glu-58 to Glu-82.			

50	HLHCR16	910123	60	2 - 3418	204	<p>Pro-9 to Pro-15, Gly-49 to Trp-54, Ser-91 to Phe-96, Thr-109 to Asp-115, Cys-124 to Ile-130, Cys-164 to Trp-169, Thr-193 to Asp-207, Thr-215 to Tyr-220, Thr-228 to Ser-240, Glu-269 to Ser-276, Glu-327 to Ala-334, Asn-376 to Asp-392, Gln-420 to Asn-428, Tyr-547 to Ser-566, Ala-616 to Gly-623, Pro-625 to Ser-631, Ser-647 to Val-653, Gly-676 to Pro-681, Tyr-720 to Glu-740, Ile-742 to Lys-748, Asp-792 to Cys-804, Leu-841 to Val-848, Gln-850 to Gly-857, Asp-879 to Gly-886, His-906 to Trp-913, Pro-968 to Thr-975, Gln-1051 to Ser-1057, Pro-1092 to Cys-1099, Lys-1113 to Cys-1120,</p>	<p>AR050: 9, AR061: 2, AR054: 2, AR089: 2, AR051: 2 L0754: 14, L0777: 13, H0553: 10, L0600: 7, L0748: 6, L0803: 4, L0749: 4, UNKWN: 4, H0624: 3, S0280: 3, S0126: 3, L0747: 3, S0282: 2, H0024: 2, H0030: 2, H0031: 2, H0040: 2, L0438: 2, S0028: 2, L0743: 2, L0596: 2, L0603: 2, S0212: 1, H0270: 1, H0244: 1, H0427: 1, H0251: 1, H0309: 1, S0338: 1, S0340: 1, S0250: 1, H0252: 1, H0039: 1, L0143: 1, H0038: 1, L0659: 1, L0565: 1, H0593: 1, H0684: 1, H0518: 1, S0390: 1, S0260: 1 and H0506: 1.</p>
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51	HFKJO15	910828	61	3 - 539	205	276	Trp-1126 to Phe-1139, Pro-9 to Pro-15, Gly-49 to Trp-54, Ser-91 to Phe-96, Thr-109 to Asp-115, Cys-124 to Ile-130, Cys-164 to Trp-169, Thr-193 to Asp-207, Thr-215 to Tyr-220, Thr-228 to Ser-240, Glu-269 to Ser-276, Glu-327 to Ala-334, Asn-376 to Asp-392, Gln-420 to Asn-428.	AR061: 0, AR089: 0 L0769: 3, L0803: 3, L0748: 3, L0749: 3, H0574: 2, H0046: 2, H0620: 2, L0794: 2, L0776: 2, L0659: 2, L0439: 2, L0754: 2, L0747: 2, L0777: 2, L0755: 2, L0605: 2, L0593: 2, H0686: 1, S0360: 1, L0717: 1, H0069: 1, H0575: 1, H0546: 1, H0024: 1, S0388: 1, H0510: 1, H0266: 1, H0644: 1, H0163: 1, H0090: 1,
							Ser-1 to Phe-13, Ala-15 to Gln-22, Pro-39 to Cys-50, Gly-58 to Gln-69, Pro-84 to Asp-92, Tyr-100 to Cys-117, Lys-123 to Ala-129, Asp-134 to Asp-148, Gly-157 to Arg-167.	

52	HMEIS32	1164006	62	2 - 1477	206	Ile-89 to Gly-106, Pro-161 to Glu-174, Ser-192 to Pro-205, Gln-231 to Arg-238, Asp-246 to Arg-262, Leu-285 to Ser-310, Ala-323 to Glu-344, Arg-384 to Pro-394, Leu-416 to Ser-428, Arg-436 to Asp-450, Ser-475 to Gly-486.	H0634: 1, H0561: 1, H0695: 1, L0763: 1, L0804: 1, L0774: 1, L0775: 1, L0783: 1, L0809: 1, L0666: 1, L0665: 1, L0438: 1, H0658: 1, H0539: 1, S0152: 1, H0522: 1, L0740: 1, L0757: 1, L0603: 1, S0276: 1 and H0542: 1. AR089: 0, AR061: 0 H0593: 3, H0694: 3, S0376: 2, S0222: 2, H0545: 2, H0561: 2, H0658: 2, H0556: 1, H0587: 1, H0318: 1, H0581: 1, H0266: 1, H0622: 1, H0063: 1, H0551: 1, H0623: 1, L0763: 1, L0637: 1, L0794: 1, L0375: 1, L0666: 1, L0663: 1, H0435: 1, H0672: 1, L0748: 1, L0758: 1, H0665: 1 and S0196: 1.				
53	HOCDR01	911439 1133383	133 63	69 - 413 2 - 1054	277 207		AR054: 7, AR089: 2, AR061: 2, AR051: 1, AR050: 0				

54	HISBG28	919899	134	3 - 977	278	Cys-49 to Leu-55, Glu-62 to Glu-68, Phe-100 to Lys-106, Pro-122 to Gln-127, Leu-219 to Gly-225, Gly-273 to Gly-281.	L0662: 3, L0653: 3, L0648: 2, L0659: 2, L0666: 2, H0435: 2, S0376: 1, H0550: 1, H0264: 1, S0472: 1, L0800: 1, L0643: 1, L0649: 1, L0803: 1, L0790: 1, H0672: 1, S0328: 1, L0779: 1 and S0260: 1.		
		947085	135	2 - 967	279	Cys-46 to Leu-52, Glu-59 to Glu-65.			
		1180262	64	1 - 1296	208	Pro-47 to Ala-58, Tyr-61 to Thr-67, Glu-86 to Ser-92, Tyr-125 to Phe-132, Asp-145 to Gln-151, Glu-211 to Tyr-219, Leu-312 to Glu-319, Ile-331 to Tyr-337, Ser-381 to Thr-389, Gly-396 to His-403.			
							AR061: 0, AR089: 0 L0766: 10, L0779: 3, L0759: 2, S0114: 1, S0116: 1, H0431: 1, H0013: 1, H0251: 1, H0628: 1, H0646: 1, L0761: 1, L0662: 1, L0776: 1, L0665: 1, H0702: 1, H0520: 1, H0539: 1, L0749: 1, L0750: 1, H0444: 1, H0445: 1 and H0543: 1.		

55	HBJIG82	920850	136	184 - 816	280	Leu-91 to Glu-98, Ile-110 to Tyr-116, Ser-160 to Thr-168, Gly-175 to His-182.	AR089: 26, AR061: 15 S0010: 1 and H0318: 1.		
		1151379	65	1 - 432	209	Phe-42 to Arg-48, Ser-91 to Lys-108, Gln-115 to Gln-122, Ser-135 to His-141.			
		924605	137	3 - 1010	281	Phe-39 to Arg-45.			
56	HBMXS88	1162642	66	281 - 1357	210	Glu-77 to Asn-82, Ser-125 to Gly-130, Gln-144 to Lys-153, Asp-173 to Ser-180, Leu-191 to Glu-197, Glu-201 to Phe-209, Ser-264 to Pro-269, Phe-282 to Ala-287, Leu-318 to Ala-325, Lys-340 to Thr-350.	AR089: 2, AR061: 2 L0766: 7, L0749: 5, L0770: 3, L0747: 3, H0650: 2, S0116: 2, H0039: 2, H0622: 2, H0264: 2, H0059: 2, L0794: 2, L0804: 2, L0805: 2, L0776: 2, L0439: 2, L0752: 2, L0731: 2, L0759: 2, H0624: 1, H0170: 1, H0656: 1, S0045: 1, S0222: 1, H0575: 1, T0082: 1, H0545: 1, H0373: 1, S0024: 1, H0252: 1, H0428: 1, H0674: 1, H0090: 1, H0616: 1, H0551: 1, L0772: 1, L0646: 1, L0641: 1, L0375: 1, L0806: 1, L0657: 1,		

57	HE8UL90	926722	138	3 - 545	282			L0789: 1, L0665: 1, H0547: 1, H0659: 1, H0521: 1, L0748: 1, L0757: 1, L0758: 1, S0026: 1, H0667: 1 and S0424: 1.		
		1226071	67	475 - 2286	211	Gly-27 to Asp-34, Cys-109 to Ser-118, Asp-129 to Gly-140, Pro-159 to Cys-175, Glu-192 to Glu-203, Ser-208 to Gly-214, Glu-246 to Cys-262, Leu-265 to Cys-271, Pro-274 to Ser-289, Asn-411 to Glu-416, Cys-520 to Arg-536, Tyr-544 to His-549, Met-572 to Thr-579, Lys-591 to Thr-596.	AR061: 4, AR050: 3, AR054: 1, AR089: 1, AR051: 1 H0013: 1			
58	HWHGF95	942749	139	3 - 641	283					
		1152274	68	1 - 753	212	Glu-29 to Trp-37, Trp-80 to Gln-87, Pro-98 to Asp-112, Glu-195 to Gly-206, Pro-225 to Ala-233.	AR050: 3, AR061: 2, AR054: 2, AR089: 1, AR051: 0 H0586: 1 and L0376: 1.			
		947019	140	2 - 742	284	Glu-25 to Trp-33, Trp-76 to Gln-83, Pro-94 to Asp-108.				

59	HNKAZ51	1152347	69	1 - 879	213	Gln-80 to Gln-86, Gln-105 to Gln-112, Gly-192 to Gln-200, Pro-215 to Ile-222, Gly-265 to Gly-275. Arg-11 to Arg-18, Gln-96 to Gln-102, Gln-121 to Gln-128.	AR050: 2, AR061: 1, AR089: 0, AR054: 0, AR051: 0 L0015: 1 and S0330: 1.		
		947067	141	31 - 612	285	Ser-25 to Ser-30, Leu-56 to Pro-63, Gln-138 to Gly-158.			
60	HFKKE19	1127465	70	580 - 2	214	Pro-18 to Met-23, Asp-65 to Glu-70, Pro-81 to Pro-88.	AR061: 6, AR089: 4 H0620: 2, H0539: 2, H0619: 1 and L0666: 1.		
		947418	142	1 - 288	286	Arg-1 to Trp-12, Ser-35 to Cys-40, Ala-72 to Thr-77, Phe-118 to Gln-124, Asn-140 to Asn-146.			
61	HILBH66	1048931	71	2 - 439	215		AR061: 19, AR089: 11 L0794: 10, L0803: 6, L0777: 6, L0758: 5, L0747: 4, L0770: 3, L0809: 3, L0666: 3, L0759: 3, L0763: 2, L0804: 2, L0783: 2, H0659: 2, L0749: 2, L0750: 2, L0779: 2, T0002: 1, H0686: 1, S0116: 1, H0483: 1, H0486: 1, L0471: 1, S0388: 1, H0083: 1, H0535: 1, H0646: 1, S0002: 1, L0761: 1,		

50

64	HUSXE73	1127979	74	3 - 863	218	Gly-43 to Arg-57, Pro-104 to Gly-111, Pro-124 to Cys-131, Gln-133 to Arg-138, Pro-140 to Gly-161, Lys-211 to Ser-219, Ser-282 to Ser-287.	AR089: 21, AR061: 9 L0794: 11, L0803: 5, L0747: 5, L0750: 5, H0618: 4, L0789: 4, L0754: 4, L0749: 4, H0625: 3, L0804: 3, L0809: 3, L0731: 3, S0046: 2, H0333: 2, H0553: 2, H0509: 2, L0659: 2, L0663: 2, L0743: 2, L0777: 2, L0755: 2, H0255: 1, H0662: 1, S0045: 1, S0222: 1, H0497: 1, H0486: 1, S0280: 1, H0309: 1, H0150: 1, H0081: 1, T0003: 1, H0083: 1, H0510: 1, H0266: 1, H0622: 1, H0424: 1, S0366: 1, H0135: 1, H0412: 1, H0413: 1, S0472: 1, H0649: 1, L0770: 1, L0646: 1, L0768: 1, L0774: 1, L0775: 1, L0666: 1, S0378: 1, S0380: 1, L0758: 1 and L0759: 1.		
		953246	146	1 - 864	290	Gly-44 to Arg-58, Pro-105 to Gly-112.			

65	HNFCS26	899406	75	2 - 994	219	<p>Pro-125 to Cys-132, Gln-134 to Arg-139, Pro-141 to Gly-162, Lys-212 to Ser-220, Ser-283 to Ser-288.</p> <p>Cys-40 to Asn-46, Gln-283 to Trp-291, Ser-298 to Tyr-305, Leu-307 to Gly-320, Gln-326 to Tyr-331.</p>	<p>AR054: 17, AR051: 12, AR050: 9, AR061: 4, AR089: 1 H0271: 6, H0556: 5, L0748: 5, L0803: 4, H0411: 3, H0586: 3, H0036: 3, L0666: 3, H0222: 2, S0212: 2, H0075: 2, H0575: 2, H0046: 2, H0071: 2, S0003: 2, H0615: 2, L0483: 2, H0623: 2, H0494: 2, L0659: 2, L0565: 2, S0380: 2, H0521: 2, L0740: 2, L0731: 2, S0194: 2, H0265: 1, S0418: 1, H0580: 1, H0587: 1, H0069: 1, H0427: 1, H0599: 1, H0004: 1, H0581: 1, T0115: 1, H0024: 1, S0362: 1, H0355: 1, H0375: 1, H0266: 1, H0687: 1, H0028: 1, S0250: 1,</p>
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						H0252: 1, H0328: 1, L0055: 1, H0212: 1, H0598: 1, H0056: 1, H0132: 1, H0647: 1, S0142: 1, H0529: 1, L0369: 1, L0372: 1, L0646: 1, L0773: 1, L0774: 1, L0607: 1, L0515: 1, L0788: 1, L0665: 1, H0144: 1, H0702: 1, S0126: 1, H0689: 1, H0690: 1, H0684: 1, H0435: 1, S0328: 1, S0378: 1, H0478: 1, H0626: 1, S3012: 1, S0027: 1, S0028: 1, S0206: 1, L0608: 1, S0192: 1 and H0543: 1.
						</

66	HCE3H08	959861	76	24 - 713	220	<p>Gly-249 to Pro-254.</p> <p>Ala-17 to Pro-24, Pro-34 to Pro-48, Lys-55 to Lys-69, Ser-89 to Asp-94, Gly-102 to Gly-110, Glu-135 to Arg-142, Ile-163 to Glu-168, Ala-200 to Thr-205.</p>	<p>AR061: 2, AR089: 2 L0761: 10, H0599: 4, L0438: 4, L0748: 4, L0770: 3, L0766: 3, L0740: 3, H0052: 2, L0764: 2, L0659: 2, S0053: 2, L0749: 2, L0779: 2, L0752: 2, L0755: 2, L0757: 2, H0656: 1, S0212: 1, H0638: 1, S0420: 1, H0675: 1, H0393: 1, H0486: 1, H0318: 1, H0581: 1, H0251: 1, H0596: 1, H0009: 1, H0373: 1, H0428: 1, H0030: 1, H0644: 1, H0674: 1, H0623: 1, H0494: 1, H0560: 1, S0002: 1, L0769: 1, L0771: 1, L0774: 1, L0807: 1, L0515: 1, L0789: 1, L0790: 1, L0791: 1, L0792: 1, L0666: 1, S0216: 1, S0374: 1, H0547: 1, H0519: 1, S0126: 1, H0660: 1, S0044: 1, L0754: 1, L0756: 1,</p>
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67	HETKR83	1225819	77	52 - 1488	221	Pro-15 to Arg-20, Arg-25 to Leu-30, Gln-53' to Trp-68, Glu-71 to Arg-76, Ala-81 to Gly-93, Gly-129 to Glu-134, Arg-171 to Arg-176, Thr-276 to Cys-282, Gly-284 to Glu-299, Lys-377 to Lys-387, Ser-392 to Cys-405, Gly-418 to Tyr-441.	L0758: 1, S0196: 1 and H0542: 1. AR089: 2, AR061: 2 H0046: 44, H0135: 11, H0539: 10, L0455: 7, S0010: 3, L0456: 3, L0750: 3, L0663: 2, L0746: 2, L0747: 2, L0779: 2, L0777: 2, H0624: 1, S0116: 1, H0208: 1, L0717: 1, H0549: 1, H0333: 1, H0013: 1, S0346: 1, L0157: 1, T0006: 1, H0652: 1, L0666: 1, H0144: 1, S0328: 1, H0696: 1 and L0439: 1.		
		963274	150	2 - 445	294	His-2 to Cys-15, Lys-46 to Lys-56, Ser-61 to Cys-74, Gly-87 to Tyr-110, Gln-127 to Tyr-146.			
68	HCUAZ04	1207329	78	575 - 276	222	Ala-1 to Tyr-10, Arg-42 to Val-48, Glu-84 to Gly-98.	AR089: 1, AR061: 0 L0769: 8, L0748: 4, L0759: 4, H0038: 3, L0750: 3, L0755: 3, H0556: 2, S0356: 2, H0574: 2, L0163: 2, L0766: 2, L0776: 2, L0663: 2, L0752: 2,		

69	HCE3J83	965585	151	546 - 214	295	Lys-6 to Phe-11.	L0731: 2, L0599: 2, H0255: 1, H0306: 1, H0125: 1, S0376: 1, H0580: 1, H0455: 1, H0497: 1, H0331: 1, L0021: 1, H0004: 1, H0618: 1, S0010: 1, H0546: 1, H0545: 1, H0123: 1, H0081: 1, H0578: 1, H0051: 1, H0510: 1, H0188: 1, H0617: 1, H0032: 1, H0169: 1, T0042: 1, L0475: 1, H0560: 1, H0132: 1, L0770: 1, L0372: 1, L0764: 1, L0771: 1, L0774: 1, L0783: 1, L0665: 1, L0438: 1, S0028: 1, L0439: 1, L0740: 1, L0786: 1, L0779: 1, L0757: 1, L0758: 1, L0588: 1, L0605: 1, S0192: 1 and S0276: 1.	AR089: 4, AR061: 3 H0266: 3, H0031: 2, H0519: 2, L0591: 2, L0593: 2, H0650: 1, S0116: 1, S0468: 1,	
		968823	79	161 - 553	223	Asn-6 to Asp-15, Glu-77 to Arg-83.			

70	HAPO167	971184	80	1 - 1983	224	<p>Asp-4 to Gln-11, Gln-31 to Lys-39, Thr-50 to Gly-63, Asn-75 to Pro-82, Ser-113 to Leu-141, Thr-160 to Ile-166, Leu-186 to Lys-192, Asn-211 to Thr-218, Glu-265 to Asp-270, Lys-317 to Gly-329, Gln-613 to Trp-621, Ser-628 to Tyr-635, Leu-637 to Gly-650, Gln-656 to Tyr-661.</p>	<p>H0393: 1, H0013: 1, H0052: 1, T0110: 1, H0050: 1, H0271: 1, H0038: 1, H0412: 1, T0041: 1, T0042: 1, H0494: 1, L0475: 1, S0150: 1, L0791: 1, H0631: 1 and L0759: 1, AR054: 10, AR061: 6, AR051: 3, AR050: 3, AR089: 1 L0768: 3, H0670: 3, L0731: 3, L0759: 3, S0192: 3, H0657: 2, H0013: 2, H0271: 2, S0003: 2, L0766: 2, L0666: 2, L0747: 2, L0749: 2, L0752: 2, H0686: 1, S0114: 1, S0356: 1, S0358: 1, S0360: 1, H0580: 1, S0132: 1, H0331: 1, L0021: 1, H0042: 1, H0575: 1, H0050: 1, H0024: 1, H0355: 1, H0375: 1, H0059: 1, H0633: 1, S0142: 1, S0210: 1, L0770: 1, L0667: 1, L0662: 1, L0804: 1, L0775: 1,</p>		
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71	HE8NI05	1216548	81	3 - 1436	225						L0776: 1, L0661: 1, L0809: 1, S0374: 1, H0519: 1, S0126: 1, H0660: 1, H0521: 1, S0044: 1, H0576: 1, L0748: 1, L0756: 1, L0596: 1, L0590: 1, L0592: 1, L0601: 1 and S0242: 1.		
											AR051: 25, AR054: 9, AR050: 3, AR061: 3, AR089: 1 L0666: 3, L0776: 2, L0750: 2, S0222: 1, H0497: 1, H0013: 1, H0009: 1, S0214: 1, H0124: 1, H0090: 1, L0792: 1, H0547: 1, H0519: 1, H0659: 1, L0777: 1, L0758: 1, L0589: 1 and L0608: 1.		
											Cys-7 to Trp-18, Pro-21 to Asn-28, Met-31 to Arg-41, Pro-47 to His-57, Pro-59 to Asn-66, Pro-72 to Cys-82, Asp-90 to Asn-103, Arg-161 to Tyr-168, Arg-217 to Trp-222, Arg-230 to Gly-235, Gln-251 to His-261, Glu-270 to Asp-282, Ser-314 to Gly-322, Ala-324 to Asp-329, Ser-367 to Asn-381, Val-383 to Asp-391, Asp-400 to Ser-411, Ser-419 to Arg-447, Leu-465 to Asp-472.		
		971303	152	73 - 609	296								
72	HHENW06	1040263	82	1123 - 2208	226						AR050: 83, AR051: Pro-10 to Gly-23,		

Ala-31 to Gly-37, Lys-68 to Tyr-76, Gln-82 to Asn-89, Val-109 to Tyr-117, Pro-124 to Cys-134, Gly-161 to Trp-171, Pro-175 to Cys-180, Pro-183 to Trp-198, Cys-221 to Gln-232, Arg-234 to Ser-243, Pro-246 to Asp-257, Lys-265 to Asp-278, Ala-348 to His-353.	81, AR054: 70, AR089: 1, AR061: 0 H0549: 7, L0665: 6, L0751: 6, L0439: 5, H0620: 3, L0803: 3, L0777: 3, L0601: 3, H0483: 2, H0486: 2, H0309: 2, L0774: 2, L0657: 2, L0659: 2, L0809: 2, L0666: 2, L0438: 2, H0520: 2, H0658: 2, L0602: 2, H0555: 2, H0624: 1, H0686: 1, H0295: 1, H0656: 1, S0282: 1, H0255: 1, S0354: 1, H0580: 1, H0619: 1, H0618: 1, H0581: 1, S0049: 1, H0052: 1, H0562: 1, H0012: 1, H0083: 1, H0687: 1, S0250: 1, H0428: 1, L0483: 1, H0135: 1, S0038: 1, H0494: 1, L0640: 1, L0638: 1, L0637: 1, L0771: 1, L0662: 1, L0805: 1, L0655: 1, L0629: 1, L0368: 1, L0789: 1, L0663: 1, H0519: 1.
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73	HNSMB24	971310	153	687 - 1271	297	Ser-15 to Tyr-24, Met-47 to Tyr-56, Gly-127 to Ser-133.	AR089: 34, AR061: 19 L0664: 2, H0483: 1, S0376: 1, L0762: 1, L0638: 1, L0771: 1, L0657: 1, L0783: 1, L0665: 1, H0658: 1, H0670: 1 and L0779: 1.	H0593: 1, H0682: 1, H0670: 1, H0521: 1, H0522: 1, H0696: 1, L0740: 1, L0779: 1 and H0667: 1.		
		971537	83	3 - 677	227		AR061: 6, AR089: 6, AR051: 3, AR050: 2, AR054: 1			
74	HLMDO77	974855	84	32 - 547	228					
		974856	154	403 - 215	298	Gly-1 to Cys-9, Pro-12 to Pro-36.				

[39] The first column in Table 1A provides the gene number in the application corresponding to the clone identifier. The second column in Table 1A provides a unique "Clone ID NO:Z" for a cDNA clone related to each contig sequence disclosed in Table 1A. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X was determined by directly sequencing the referenced clone. The reference clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein.

[40] The third column in Table 1A provides a unique "Contig ID" identification for each contig sequence. The fourth column provides the "SEQ ID NO:" identifier for each of the contig polynucleotide sequences disclosed in Table 1A. The fifth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred open reading frame (ORF) shown in the sequence listing and referenced in Table 1A, column 6, as SEQ ID NO:Y. Where the nucleotide position number "To" is lower than the nucleotide position number "From", the preferred ORF is the reverse complement of the referenced polynucleotide sequence.

[41] The sixth column in Table 1A provides the corresponding SEQ ID NO:Y for the polypeptide sequence encoded by the preferred ORF delineated in column 5. In one embodiment, the invention provides an amino acid sequence comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by "ORF (From-To)". Also provided are polynucleotides encoding such amino acid sequences and the complementary strand thereto.

[42] Column 7 in Table 1A lists residues comprising epitopes contained in the polypeptides encoded by the preferred ORF (SEQ ID NO:Y), as predicted using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, at least one, two, three, four, five or more of the predicted epitopes as described in Table 1A.

It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly.

[43] Column 8 in Table 1A provides an expression profile and library code: count for each of the contig sequences (SEQ ID NO:X) disclosed in Table 1A, which can routinely be combined with the information provided in Table 4 and used to determine the tissues, cells, and/or cell line libraries which predominantly express the polynucleotides of the invention. The first number in column 8 (preceding the colon), represents the tissue/cell source identifier code corresponding to the code and description provided in Table 4. For those identifier codes in which the first two letters are not "AR", the second number in column 8 (following the colon) represents the number of times a sequence corresponding to the reference polynucleotide sequence was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ^{33}P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression.

[44] Column 9 in Table 1A provides a chromosomal map location for certain polynucleotides of the invention. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for

Biotechnology Information) UniGene database. Each sequence in the UniGene database is assigned to a "cluster"; all of the ESTs, cDNAs, and STSs in a cluster are believed to be derived from a single gene. Chromosomal mapping data is often available for one or more sequence(s) in a UniGene cluster; this data (if consistent) is then applied to the cluster as a whole. Thus, it is possible to infer the chromosomal location of a new polynucleotide sequence by determining its identity with a mapped UniGene cluster.

[45] A modified version of the computer program BLASTN (Altschul et al., J. Mol. Biol. 215:403-410 (1990); and Gish and States, Nat. Genet. 3:266-272 (1993)) was used to search the UniGene database for EST or cDNA sequences that contain exact or near-exact matches to a polynucleotide sequence of the invention (the 'Query'). A sequence from the UniGene database (the 'Subject') was said to be an exact match if it contained a segment of 50 nucleotides in length such that 48 of those nucleotides were in the same order as found in the Query sequence. If all of the matches that met this criteria were in the same UniGene cluster, and mapping data was available for this cluster, it is indicated in Table 1A under the heading "Cytologic Band". Where a cluster had been further localized to a distinct cytologic band, that band is disclosed; where no banding information was available, but the gene had been localized to a single chromosome, the chromosome is disclosed.

[46] Once a presumptive chromosomal location was determined for a polynucleotide of the invention, an associated disease locus was identified by comparison with a database of diseases which have been experimentally associated with genetic loci. The database used was the Morbid Map, derived from OMIM™ (*supra*). If the putative chromosomal location of a polynucleotide of the invention (Query sequence) was associated with a disease in the Morbid Map database, an OMIM reference identification number was noted in column 10, Table 1A, labelled "OMIM Disease Reference(s)". Table 5 is a key to the OMIM reference identification numbers (column 1), and provides a description of the associated disease in Column 2.

TABLE 1B

Clone ID NO:Z	SEQ ID NO:X	CONTIG ID:	BAC ID: A	SEQ ID NO:B	EXON From-To
HNGER43	15	699391	AC023328	299	1-383
HTKAA03	52	961002	AC073152	300	1-465
HTKAA03	52	961002	AC073152	301	1-638
HTTKB18	53	963346	AC012186	302	1-101 1432-1773 2108-2234 2755-2942 4452-4677 6207-6294 6910-7030 8184-8720 8935-9043 9126-9538 9680-10164 11135-11344 11744-11906 14393-14679 20063-20220 20444-20625 20961-21364 21744-21893 22016-22076 22652-22911 22942-24288 24334-25010 25159-25619
HFKJO15	61	910828	AC005500	303	1-180 288-509 638-770 1363-1466 1541-1661 1829-1971 1988-2162 3576-3797 4349-4491 4913-6610
HFKJO15	61	910828	AC007731	304	1-180 288-509 638-770 1363-1466 1541-1661 1829-1971 1988-2162

					3576-3797 4349-4491 4913-6610
HFKJO15	61	910828	AC005500	305	1-97 305-602
HFKJO15	61	910828	AC007731	306	1-97 305-602
HCE3J83	79	968823	AC015841	307	1-161
HNSMB24	83	971537	AC015555	308	1-61 464-586 752-1423 3455-3587 5766-5958 6757-7115 8075-8329 8778-8876 12309-12455 13123-13279 16212-17107
HNSMB24	83	971537	AP001623	309	1-61 464-586 752-1423 3455-3580 4976-5021 5793-5958 6757-7115 8075-8329 8778-8876 12305-12451 13119-13275 16208-17104
HNSMB24	83	971537	AC015555	310	1-674
HNSMB24	83	971537	AP001623	311	1-674

[47] Table 1B summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

TABLE 2

Clone ID NO:Z	Contig ID:	SEQ ID NO:X	Analysis Method	PFam/NR Description	PFam/NR Accession Number	Score/ Percent Identity	NT From	NT To
HPLBY29	509875	85	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	4.49	284	138
HOUEU57	531182	86	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	4.52	105	149
HNHFR39	576399	87	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	4.45	237	284
HFATE17	662491	88	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	5.17	458	526
HNGER43	699391	15	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	3.79	151	195
HWAAE95	789051	89	HMMER 1.8	PFAM: EGF-like domain	PF00008	14.74	108	176
HMSG27	855759	90	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	5.56	276	202
HKIXB77	870018	91	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	5.34	264	326
HTNBM01	910705	92	HMMER 1.8	PFAM: EGF-like domain	PF00008	18.51	232	339
			blastx.2	Low density lipoprotein receptor related protein- deleted 1	sp AAF70379 AAF70 379	96% 30% 31% 100% 23%	7 7 34 577 1	366 342 342 651 342

						30%	342	575
						35%	46	255
						36%	46	243
						27%	46	324
						28%	46	279
						30%	46	249
						27%	19	273
						28%	76	246
						31%	46	234
						31%	13	117
						31%	202	363
						22%	19	264
						40%	43	138
						31%	166	306
						31%	37	246
						25%	79	312
						30%	175	264
						27%	31	171
						41%	55	105
						32%	46	129
						26%	16	141
HBJGT92	919507	93	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	7.68	377	436
HAGAT56	924588	94	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	4.58	54	119
HCFMG57	1205913	22	blastx.14	HYPOTHETICAL 135.2 KDA PROTEIN.	sp Q9Y4J9 Q9Y4J9	62%	2	208
HCFMG57	929803	95	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	3.89	661	678
HTEHS55	933264	96	HMMER	PFAM: Bacterial mutT	PF00293	6.06	255	284

HMUBI13	1189811	24	1.8 blastx.14	protein isomerase like protein [Arabidopsis thaliana]	gi 5302783 emb CAB 46032.1	51% 62% 50%	298 835 73	828 945 132
HMUBI13	937820	97	HMMER 2.1.1 blastx.2	PFAM: Fumarylacetoacetate (FAA) hydrolase family Brain cDNA, clone MNCb-4134.	PF01557	288.8	327	830
HPCAO89	1137858	25	blastx.14	serpin [Equus caballus]	sp BAA95083 BAA9 5083	87%	237	899
HPCAO89	946913	98	HMMER 1.8 blastx.2	PFAM: Serpins (serine protease inhibitors) leupin [Homo sapiens]	gi 164241 gb AAA97 513.1 PF00079	45% 47% 53.12	93 612 94	596 1022 309
HE2KN09	1163877	26	blastx.14	(AF095446) syndesmos [Gallus gallus]	emb CAA61420.1	39% 45% 69%	82 309 30	327 452 686
HE2KN09	951647	99	HMMER 1.8 blastx.2	PFAM: Bacterial mutT protein Syndesmos.	PF00293	7.21	171	230
HCWGE12	967067	100	HMMER 1.8	PFAM: Bacterial mutT protein	sp AAF29566 AAF29 566	69%	24	680
HCEPY32	530520	101	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	4.04	214	288
HSVCH37	558195	102	HMMER 2.1.1	PFAM: 3'-cyclic nucleotide phosphodiesterase	PF00233	5.18 30	245 18	313 98
HOFNL18	666498	103	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	4.34	286	345

HTOCG37	708888	104	HMMER 2.1.1	PFAM: 3'-cyclic nucleotide phosphodiesterase	PF00233	65.1	42	215
			blastx.2	3',5'-cyclic-nucleotide phosphodiesterase (EC 3.1.4.17) 8B, 1	pir JE0293 JE0293	100% 53%	6 179	203 340
HTEOF80	847224	105	HMMER 1.8	PFAM: EGF-like domain	PF00008	14.65	20	100
			blastx.2	Epidermal growth factor repeat containing protein.	sp AAF27812 AAF27 812	96%	11	106
HSLDP32	1182295	33	blastx.14	ZK688.3 protein [Escherichia coli]	gi 4062757 dbj BAA3 6014.1	100%	389	3
HSLDP32	866241	106	HMMER 2.1.1	PFAM: Fumarylacetoacetate (FAA) hydrolase family	PF01557	39.8	78	197
			blastx.2	conserved hypothetical protein PA0318 [imported] - Pseudomonas aeruginosa (strain PAO1)	pir G83604 G83604	55% 40%	197 12	346 188
HAICQ62	1182256	34	blastx.14	(AF201831) FIL1 epsilon [Homo sapiens]	gi 6694390 gb AAF25 211.1 AF201831.1	62% 50%	138 498	503 575
HAICQ62	888225	107	HMMER 2.1.1	PFAM: Interleukin-1	PF00340	42.1	388	663
HRDBE43	894862	35	HMMER 2.1.1	PFAM: Laminin G domain	PF00054	195.2	191	580
			blastx.2	CG8403 PROTEIN.	sp Q9V714 Q9V714	33% 37% 36% 26% 47%	2 35 764 173 686	1288 823 1285 607 730

HRDBE43	947966	108	HMMER 1.8 blastx.14	PFAM: Laminin G domain perlecan [Mus musculus]	PF00054 gj200296 gb AAA39 911.1	102.93	1023	661
						46%	963	640
						31%	1627	1250
						38%	1624	1361
						38%	1630	1379
						40%	966	715
						32%	957	661
						72%	1696	1643
						41%	1203	1132
						47%	1840	1772
						33%	1182	1111
						50%	1242	1189
						47%	1834	1784
						45%	1867	1796
						47%	1864	1814
						57%	1182	1141
						53%	1834	1796
						61%	1020	982
						44%	1194	1141
						50%	1834	1793
						63%	1828	1796
						66%	1227	1201
						53%	1834	1796
						46%	1239	1201
						47%	1188	1138
						31%	1699	1643
						40%	1538	1494
						66%	1185	1159
						54%	1828	1796

HSSKD85	908141	36	HMMER 2.1.1	PFAM: EGF-like domain	PF00008	45%	1828	1796
			blastx.2	EGF repeat transmembrane protein - mouse	pir T30176 T30176	60%	1227	1198
HCRMV17	1180333	37	blastx.14	KIF3B protein [Mus musculus]	gi 1060923 dbj BAA0 5070.1	27%	1158	1060
						42%	1023	982
HCRMV17	910010	109	HMMER 2.1.1	PFAM: Kinesin motor domain	PF00225	129.2	812	910
			blastx.14	KIF3B protein [Mus musculus]	gi 1060923 dbj BAA0 5070.1	89%	332	1006
HFOXL77	1137799	38	blastx.14	Xotch protein [Xenopus laevis]	gi 1364263 gb AAB0 2039.1	40%	356	787
						36%	186	335
						72%	579	1463
						98%	4	330
						100%	445	531
						42%	457	513
						50%	445	468
						225.4	3	317
						100%	3	317
						63%	432	614
						42%	444	500
						50%	432	455
						42%	133	303
						62%	190	285
						50%	178	285
						50%	133	234
						42%	190	303
						46%	190	285
						53%	193	270
						46%	190	285
						41%	178	270
						46%	193	282

								43%	193	303
								41%	169	285
								38%	178	303
								52%	193	267
								41%	193	285
								50%	193	270
								42%	193	270
								40%	193	282
								76%	133	171
								38%	133	210
								52%	266	334
								60%	290	334
								32%	217	300
								53%	133	171
								33%	133	204
								57%	293	334
								53%	290	334
								50%	133	168
								50%	133	168
								42%	293	334
								66%	142	168
								54%	305	337
								75%	247	270
								29%	266	337
								50%	133	168
								50%	133	168
								50%	133	168
								29%	133	204
								50%	133	168
								50%	133	168
								50%	305	334

HFOXL77	910698	110	HMMER 2.1.1	PFAM: EGF-like domain	PF00008	51	38%	133	171
			blastx.2	CELL SURFACE PROTEIN.			sp O35516 O35516	43%	285
							45%	302	334
							29%	133	204
							66%	308	334
							45%	302	334
							62%	133	156
							41%	133	168
							38%	133	171
							45%	299	331
							35%	293	334
							40%	302	346
							42%	229	270
							55%	308	334
							50%	148	171
							26%	133	201
							50%	226	255
							50%	302	337
								285	386
								285	485
								285	488
								285	485
								285	482
								285	485
								285	488
								285	485
								300	488
								285	485
								285	482
								285	485

HBXCZ29	910842	111	HMMER 1.8	PFAM: EGF-like domain	PF00008	37%	285	485
			blastx.2	Low density lipoprotein receptor related protein- deleted 1		40%	285	485
						46%	285	473
						38%	285	485
						35%	285	485
						31%	285	512
						36%	294	482
						38%	285	488
						52%	143	193
						32.85	608	718
						83%	410	805
						96%	2	319
						32%	527	802
						30%	2	292
						33%	5	487
						29%	527	802
						35%	17	250
						27%	8	316
						52%	276	464
						30%	17	283
						28%	380	718
						32%	5	256
						33%	5	244
						29%	527	811
						26%	17	298
						33%	17	232
						35%	17	247
						32%	17	223
						32%	53	253

HRDBJ38	917583	112	HMMER 2.1.1	PFAM: Trypsin	PF00089	28%	11	250
HCOKA10	907080	41	HMMER 2.1.1	SERINE PROTEASE (FRAGMENT)	sp O97658 O97658	62%	23	856
			blastx.2	PFAM: Ribosomal protein L34e	PF01199	229.8	509	213
			blastx.2	ribosomal protein L34 [Homo sapiens]	gb AAC41916.1	98%	521	216
HCOKA10	918918	113	HMMER	PFAM: Small cytokines	PF00048	124.2	1447	1238

			2.1.1	(intecrine/chemokine), interleukin-8 like					
HCOKA10	919869	114	blastx.14	granulocyte chemotactic protein, GCP-2 - bovine	pir B54188 B54188	100%	1444	1223	
			HMMER 2.1.1	PFAM: Small cytokines (intecrine/chemokine), interleukin-8 like	PF00048	124.2	169	378	
HKGDI91	1137801	42	blastx.14	(AB013440) Dll3 protein [Mus musculus]	gi 3721842 dbj BAA3 3716.1	92%	180	404	
						40%	168	293	
						47%	192	299	
						44%	324	404	
						41%	303	404	
HKGDI91	927222	115	HMMER 1.8	PFAM: EGF-like domain	PF00008	36.48	255	359	
			blastx.2	DLL3 protein precursor..	sp AAF62542 AAF62 542	100%	180	404	
						39%	111	431	
HMKBA52	937325	116	HMMER 1.8	PFAM: Bacterial mufT protein	PF00293	42%	192	404	
						4.28	223	267	
HLCMP75	1203728	44	blastx.14	Tumor endothelial marker 1 precursor.	sp AAG00867 AAG0 0867	88%	160	702	
						100%	1088	1267	
						71%	823	1089	
						100%	26	169	
						93%	708	797	
						35%	523	693	
						41%	601	693	
						45%	619	690	
						42%	702	785	
						46%	702	785	
						37%	586	690	

HLCMP75	944722	117	HMMER 2.1.1	PFAM: EGF-like domain	PF00008	33	705 256 781 32 714 548 104 592 811 823 469 583 595 592 29 414 652 820 499 898 711 828 832 607 831 702 1317 197	38% 55% 32% 62% 34% 39% 40% 31% 30% 37% 36% 31% 28% 31% 61% 50% 46% 36% 50% 50% 24% 35% 27% 29% 47% 46% 36% 41%	797 315 909 79 809 631 169 696 909 909 534 678 690 687 67 461 696 885 534 933 797 887 939 678 881 746 1382 247				
							200	33				200	304

79

							42%	307	348
HWHQR25	947020	118	HMMER 2.1.1	PFAM: EGF-like domain	PF00008		40%	367	411
			blastx.2	Notch ligand DLL4.	sp AAF76427 AAF76427		102.5	113	214
							99%	2	538
							41%	20	535
							37%	2	535
							41%	8	481
							35%	32	535
HLKAB61	1183217	46	blastx.14	cell surface protein [Mus musculus]	gi 2373395 dbj BAA22094.1		84%	159	347
							87%	324	395
							41%	198	341
							52%	333	389
							50%	237	290
							53%	249	287
							43%	237	284
							85%	333	353
							75%	330	353
							85%	333	353
							85%	333	353
							85%	333	353
							85%	333	353
							55%	375	401
							71%	333	353
							50%	333	362
							71%	333	353
							71%	333	353
							71%	333	353
HLKAB61	948002	119	HMMER 1.8	PFAM: EGF-like domain	PF00008		30.43	159	263

			blastx.2	cell-fate determining gene Notch2 protein - rat	pir A49128 A49128	86%	138	296
HEGAZ61	950033	120	HMMER 2.1.1	PFAM: Reprolysin family propeptide	PF01562	141.4	276	560
			blastx.2	epididymal apical protein I-precursor [Macaca fascicularis]	emb CAA46929.1	92%	60	560
HPJEQ52	953155	121	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	37.64	152	277
HFIZB56	1137798	49	blastx.14	developmental protein [Drosophila melanogaster]	gi 157993 gb AAA28 725.1	55%	2	412
						52%	2	409
						49%	2	415
						48%	2	406
						47%	2	406
						47%	2	415
						41%	2	409
						41%	2	409
						50%	2	328
						40%	2	379
						48%	86	409
						39%	2	415
						37%	11	415
						50%	89	412
						41%	2	376
						52%	116	409
						44%	2	343
						47%	104	409
						39%	2	313
						41%	2	238
						48%	200	415

46%	209	415
41%	116	331
47%	227	415
42%	98	301
39%	2	223
35%	212	433
37%	2	178
35%	230	409
45%	74	178
48%	314	412
41%	302	409
37%	188	298
35%	332	415
42%	332	415
45%	2	73
47%	251	313
39%	131	199
38%	23	85
38%	23	85
42%	101	178
50%	197	268
45%	248	313
42%	137	199
47%	23	73
40%	236	301
40%	77	151
40%	350	415
35%	365	415
38%	362	415
53%	83	121
53%	134	178

HFIZB56	955618	122	HMMER 2.1.1	PFAM: EGF-like domain	PF00008	40% 53% 58% 42% 46% 50% 40% 46% 39% 40% 38% 50% 33%	167 197 311 137 1214 191 77 29 8 77 83 266 108	232 235 346 178 1258 232 121 67 76 121 136 307 170
HUKEP18	1106982	50	blastx.14	(AF100707) testes-specific protein TSP50 [Homo sapiens]	gi 6652836 gb AAF22500.1 AF100707_1	100%	139	513
HUKEP18	957456	123	HMMER 1.8	PFAM: Trypsin	PF00089	82.96	729	361
HEEAN63	960233	124	blastx.2	TESTES-SPECIFIC PROTEIN TSP50.	sp Q9UI38 Q9UI38	100%	735	340
HEEAN63	960233	124	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	4.79	255	290
HEEAN63	960233	124	blastx.2	CG11095 PROTEIN.	sp Q9VY79 Q9VY79	37%	249	614

HTKAA03	961002	52	HMMER 2.1.1	PFAM: Fumarylacetoacetate (FAA) hydrolase family	PF01557	48%	149	229
			blastx.2	probable 2-hydroxyhepta- 2,4-diene-1,7-dioate isomerase b1180 - Escherichia coli		89.9	2	148
HTTKB18	963346	53	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	98%	722	853
			blastx.14	MEM3 [Mus musculus]		4.1	1352	2083
HPTZB93	1222478	54	blastx.14	CRIPTO, FRL-1, CRYPTIC FAMILY 1.	gi 1354050 gb AAB1 8153.1	83%	767	1363
			HMMER 1.8			93%	2084	2440
HPTZB93	971842	125	blastx.2	PFAM: EGF-like domain	PF00008	76%	284	736
			HMMER 1.8			80%	195	287
HTSHM38	1138085	55	blastx.2	CRIPTO, FRL-1, CRYPTIC FAMILY 1.	sp P97766 P97766	100%	745	768
			blastx.2			35%	812	871
HTSHM38	1138085	55	blastx.2	MEGF6 protein - rat	sp P97766 P97766	42%	1028	1090
			blastx.2			41%	189	239
HTSHM38	1138085	55	blastx.2	MEGF6 protein - rat	sp P97766 P97766	52%	330	755
			blastx.2			60%	279	353
HTSHM38	1138085	55	blastx.2	MEGF6 protein - rat	sp P97766 P97766	20.4	562	491
			blastx.2			55%	820	344
HTSHM38	1138085	55	blastx.2	MEGF6 protein - rat	sp P97766 P97766	69%	1	447
			blastx.2			43%	70	423
HTSHM38	1138085	55	blastx.2	MEGF6 protein - rat	sp P97766 P97766	35%	1	429
			blastx.2			35%	4	435
HTSHM38	1138085	55	blastx.2	MEGF6 protein - rat	sp P97766 P97766	33%	1	333
			blastx.2			33%	1	333

85

33%	2028	2222
48%	1419	1535
51%	2052	2156
48%	1851	1973
47%	1482	1601
34%	1812	1976
50%	1944	2057
37%	1470	1622
40%	2097	2222
48%	1500	1598
35%	1806	1982
50%	1884	1973
41%	1851	1973
51%	2040	2120
60%	1674	1748
39%	2058	2156
60%	1608	1676
48%	1500	1598
36%	1434	1532
52%	1599	1667
43%	2133	2222
44%	2136	2222
42%	2124	2222
48%	1512	1598
37%	1416	1496
50%	1935	2006
46%	1692	1775
50%	1419	1478
40%	1683	1748
36%	1659	1748
50%	1977	2036

87

HELDY60	975104	128	HMMER 2.1.1 blastx.14	PFAM: Thrombospondin type 1 domain putative [Bos taurus]	gi 508428 gb AAA74 122.1		46%	1686	1724
							70%	1752	1781
							29%	1794	1844
							71%	1761	1781
							60%	1695	1724
							70%	2007	2036
							38%	1530	1583
							20%	1398	1469
							25%	1740	1859
							57%	1374	1415
							75%	1644	1667
							31%	1794	1841
							60%	1392	1421
							33%	1548	1610
							50%	2016	2051
							24%	1515	1625
							169.6	286	438
							47%	2017	2250
							43%	2041	2247
							52%	2032	2208
							42%	1948	2157
							40%	1432	1629
							52%	1513	1650
							37%	2032	2268
							37%	2041	2280
							40%	2032	2238
							53%	1984	2100
							37%	2041	2250
							42%	2041	2208

1695	1528	37%					
2205	2041	41%					
1938	1783	40%					
1650	1525	45%					
1710	1597	52%					
2136	1984	41%					
1662	1525	43%					
2238	2032	36%					
1659	1537	46%					
1839	1705	40%					
2130	2032	54%					
1845	1705	42%					
2103	1984	42%					
1635	1450	38%					
2238	2113	50%					
1662	1489	34%					
2262	2041	33%					
1659	1534	42%					
1662	1537	38%					
1662	1537	42%					
1662	1537	42%					
1629	1537	48%					
1965	1783	36%					
2160	2038	46%					
1635	1537	39%					
1890	1780	43%					
1878	1792	51%					
1662	1495	32%					
1665	1537	32%					
2154	2041	42%					
1890	1783	41%					

48%	1537	1629
30%	1666	1845
36%	2041	2172
42%	1495	1620
57%	2164	2247
39%	1537	1659
43%	2041	2163
42%	1744	1842
45%	2032	2124
41%	1537	1629
39%	2041	2154
42%	2041	2154
41%	1534	1620
42%	2032	2145
38%	1696	1827
36%	2041	2154
38%	1537	1662
51%	2023	2109
44%	2041	2154
39%	1537	1650
29%	1450	1611
37%	1534	1629
38%	1588	1695
28%	1663	1839
39%	2041	2154
35%	1537	1653
41%	1537	1638
43%	1843	1938
44%	2161	2247
41%	1537	1629
46%	2161	2250

91

- 92

42%	1525	1587
40%	1447	1527
58%	2494	2544
44%	2014	2088
50%	1450	1509
42%	1450	1527
52%	1792	1842
58%	1792	1842
66%	2509	2544
40%	2041	2121
34%	1705	1782
50%	1705	1764
36%	1840	1938
35%	1609	1710
30%	1849	1998
47%	1984	2040
39%	1705	1788
55%	1792	1845
52%	1537	1587
43%	1705	1773
56%	1792	1839
40%	1534	1599
45%	1705	1764
53%	2164	2208
50%	2041	2094
37%	1537	1617
47%	1792	1842
56%	2161	2208
75%	2509	2544
36%	1447	1536
44%	1789	1842

94

43%	1792	1839
45%	1948	2007
47%	1888	1938
66%	2509	2544
53%	1981	2025
60%	1897	1941
50%	1792	1845
40%	2494	2568
34%	1450	1527
47%	2161	2217
50%	2503	2544
50%	1858	1893
41%	1789	1839
58%	2509	2544
41%	1981	2031
44%	1984	2037
34%	2494	2571
38%	1945	2007
42%	1981	2037
33%	1447	1527
33%	1528	1617
61%	2462	2500
36%	2032	2088
33%	1702	1773
31%	2104	2208
66%	2164	2199
50%	1792	1845
47%	2544	2594
33%	1696	1767
34%	1537	1605
25%	1948	2064

96

				45%	1789	1848
				50%	2161	2208
				42%	1705	1767
				32%	1948	2031
				46%	2550	2594
				46%	1537	1581
				42%	1603	1659
				58%	2465	2500
				47%	2494	2544
				40%	1732	1776
				70%	1666	1695
				53%	1984	2028
				50%	1738	1773
				64%	1966	2007
				38%	1792	1845
				53%	1606	1650
				47%	2544	2594
				37%	1534	1581
				38%	2494	2547
				75%	2462	2485
				50%	2503	2544
				54%	1909	1941
				47%	1705	1755
				44%	1972	2025
				54%	1666	1698
				46%	1963	2007
				63%	1666	1698
				69%	1657	1695
				80%	1666	1695
				47%	2494	2544
				53%	1666	1710

[illegible]

99

75%	2462	2485
53%	2462	2500
87%	2462	2485
75%	2462	2485
30%	2494	2562
50%	2509	2544
60%	1978	2007
43%	2547	2594
29%	2074	2154
54%	1909	1941
50%	2509	2544
42%	1972	2013
60%	1666	1695
60%	1909	1938
46%	2462	2500
71%	2462	2482
53%	1849	1887
40%	310	375
44%	1939	1992
40%	1537	1581
63%	1663	1695
40%	1666	1710
46%	1666	1710
32%	1426	1509
50%	2547	2588
66%	1741	1767
58%	1969	2004
75%	2462	2485
37%	2544	2591
43%	1615	1662
30%	1705	1782

				40%	2068	2112
				40%	1450	1515
				66%	1744	1770
				54%	1978	2010
				46%	1666	1710
				40%	1666	1710
				33%	1666	1737
				53%	1615	1659
				50%	1909	1938
				71%	1858	1878
				35%	1789	1839
				38%	1819	1881
				50%	2113	2154
				62%	2462	2485
				75%	2462	2485
				46%	2550	2594
				85%	2462	2482
				50%	2509	2544
				47%	2104	2154
				46%	2462	2500
				50%	1945	1992
				50%	1909	1938
				29%	1426	1518
				38%	2462	2500
				85%	2462	2482
				35%	2544	2594
				42%	2509	2550
				35%	2494	2544
				50%	1984	2025
				85%	2462	2482
				46%	2550	2594

32%	294	368
61%	1990	2028
41%	1447	1497
50%	1909	1938
60%	1489	1518
46%	2113	2157
41%	1909	1959
85%	2462	2482
55%	1981	2007
71%	1984	2004
33%	1609	1689
70%	1666	1695
71%	2462	2482
37%	2182	2229
40%	1666	1710
29%	1426	1506
55%	1852	1878
46%	2462	2500
42%	1939	1995
42%	1741	1782
71%	2462	2482
50%	1909	1938
46%	1444	1488
25%	139	258
46%	1495	1533
35%	2494	2544
36%	1693	1749
62%	1816	1839
85%	1984	2004
85%	2462	2482
50%	2547	2594

HNAL30	526878	129	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	4.52	80	127
HWADY16	1182316	58	blastx.14	(AC007785) BC282485_1 [Homo sapiens]	gi 5042405 gb AAD3 8244.1 AC007785 2	77% 91%	342 35	881 346
HWADY16	661322	130	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	5.3	162	206
HNTRU73	1173875	59	blastx.14	KIF3B protein [Mus musculus]	gi 1060923 dbj BAA0 5070.1	100% 72%	3 219	182 458
HNTRU73	910009	131	HMMER 2.1.1	PFAM: Kinesin motor domain	PF00225	114.5	3	188
HLHCR16	910123	60	blastx.14	KIF3B protein [Mus musculus]	gi 1060923 dbj BAA0 5070.1	73% 100%	219 3	1127 182
			HMMER 2.1.1	PFAM: Sushi domain (SCR repeat)	PF00084	744.9	197	358
			blastx.2	complement receptor 1 - chimpanzee (fragment)	pir I36936 I36936	29% 30% 31% 30% 28% 29% 29% 28% 31% 26% 27% 28% 30% 36% 29% 26%	710 1166 818 1958 710 1163 1757 1766 911 1970 1754 1166 2378 20 1244 2210	1600 1921 1636 2764 1513 1921 2632 2632 1636 3031 2605 1921 3031 562 1921 3163

26%	2210	3163
32%	11	571
32%	11	571
32%	710	1204
32%	11	562
32%	710	1204
30%	23	595
30%	992	1630
32%	710	1204
29%	23	595
36%	23	460
33%	20	460
27%	32	844
29%	728	1387
30%	983	1549
28%	728	1387
31%	713	1246
32%	2657	3124
31%	860	1387
30%	518	1228
31%	713	1246
33%	713	1117
32%	701	1114
32%	113	574
32%	113	574
31%	2417	2983
30%	1811	2242
32%	2642	3109
34%	80	460
32%	1244	1639
33%	701	1111

31%	95	547
29%	2219	2983
31%	2681	3130
29%	2618	3109
30%	734	1171
31%	1109	1537
32%	80	451
31%	2219	2761
32%	725	1114
25%	1721	2452
29%	113	574
31%	725	1114
28%	1550	2113
26%	2474	3319
30%	1472	2026
27%	1424	2113
25%	2474	3100
25%	1721	2452
27%	1100	1639
29%	893	1363
35%	11	364
26%	1721	2326
27%	2555	3322
26%	1721	2449
33%	182	574
26%	1100	1630
29%	2549	2938
30%	1997	2401
30%	38	424
32%	1241	1657
30%	626	1015

HLHCR16	965511	132	HMMER 2.1.1	PFAM: Sushi domain (SCR repeat)	PF00084			30% 25% 24% 30% 31% 31% 31% 26% 31% 31% 29% 25% 30% 22%	734 1250 1250 38 95 95 734 1769 725 725 1799 1472 593 371	1090 1852 1852 370 382 382 1090 2464 1015 1015 2056 1882 847 598
			blastx.2	furrowed [Drosophila melanogaster]						
								357.8	197	358
					gb AAB36703.1			31% 28% 34% 28% 35% 32% 34% 30% 30% 32% 27% 27% 34% 28%	638 254 737 254 89 908 692 740 419 11 17 17 1100 11	1480 1228 1387 1120 604 1468 1189 1270 1018 529 916 553 1480 445

HPKJO15	910828	61	HMMER 1.8	PFAM: Laminin EGF-like (Domains III and V)	PF00053		30%	977	1480
			blastx.14				37%	365	571
							29%	1220	1489
							20.47	18	191
							51%	12	539
							46%	69	191
							38%	12	152
							41%	78	200
							41%	99	191
							36%	417	539
							48%	465	539
							38%	78	170
							36%	63	152
							40%	246	326
							35%	246	329
							37%	381	461
							50%	12	71
							33%	246	335
							33%	276	356
							36%	474	539
							44%	12	65
							29%	150	260
							46%	381	425
							31%	183	287
							40%	246	305
							42%	378	440
							50%	285	326
							45%	111	170
							24%	285	395

HMEIS32	1164006	62	blastx.14	Pistil extensin like protein, partial CDS only [Nicotiana tabacum]	gi 19917 emb CAA78392.1	26% 40% 42% 40% 50% 62% 31%	381 243 420 330 510 3 6	470 287 476 374 539 26 71
HMEIS32	911439	133	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	32% 100% 66% 41%	123 1619 675 1222	197 1639 701 1272
HOGDR01	1133383	63	blastx.14	(AC003965) SP001LA [Homo sapiens]	gi 2734092 gb AAB93671.1	100%	242	967
HOGDR01	919899	134	HMMER 1.8	PFAM: Trypsin	PF00089	322.84	171	881
HOGDR01	947085	135	blastx.2	SP001LA (FRAGMENT).	sp O43342 O43342	99%	165	890
			HMMER 1.8	PFAM: Trypsin	PF00089	320.16	161	871
HISBG28	920850	136	blastx.2	(AC003965) SP001LA [Homo sapiens]	gb AAB93671.1	99%	155	967
			HMMER 2.1.1	PFAM: 3'-cyclic nucleotide phosphodiesterase	PF00233	195.7	187	789
HBJIG82	1151379	65	blastx.2	3',5'-cyclic-AMP phosphodiesterase (EC 3.1.4.-) - human (fragment)	pir A47286 A47286	90%	1	804
			blastx.14	similar to Drosophila	gi 1503988 dbj BAA1	100%	43	282

HBJIG82	924605	137	HMMER 2.1.1 blastx.2	melanogaster septin (sep2). [Homo sapiens] PFAM: Cell division protein Sep2 (Fragment).	3193.1 PF00735 sp AAG09408 AAG0 9408	94%	280	396
HBMXS88	1162642	66	blastx.14	(AF151811) CGI-53 protein [Homo sapiens]	gi 4929575 gb AAD3 4048.1 AF151811_1	98% 100% 100% 100%	281 749 1121 49	754 1060 1357 258
HBMXS88	926722	138	HMMER 1.8 blastx.14	PFAM: Bacterial mutT protein (AF151811) CGI-53 protein [Homo sapiens]	PF00293 gi 4929575 gb AAD3 4048.1 AF151811_1	3.8 97% 92% 78% 62% 48%	312 69 739 642 482 767	371 494 819 737 553 847
HE8UL90	942749	139	HMMER 2.1.1 blastx.2	PFAM: EGF-like domain CRUMBS HOMOLOG 1.	PF00008 sp P82279 P82279	63.9 85% 36% 33% 32% 34% 32% 34% 31% 36% 32% 32%	297 78 153 156 156 156 156 156 156 237 177 156	398 566 566 566 575 566 512 521 452 518 512 410

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HFKKE19	947418	142	HMMER 1.8		suppressor [Homo sapiens] PFAM: EGF-like domain	PF00008		33%	503	547
			blastx.2		MEGF3 (FRAGMENT).	sp Q9QYP2 Q9QYP2		98%	1	249
HILBH66	1048931	71	blastx.2		integrin alpha-E chain - human	pir A53213 A53213		78%	233	289
								28%	248	289
HILBH66	948844	143	HMMER 1.8		PFAM: Integrins alpha chain	PF00357		98%	131	439
			blastx.2		HUMINAE (Fragment).	sp AAF43107 AAF43107		83%	80	151
HWMEQ37	949568	144	HMMER 2.1.1		PFAM: Low-density lipoprotein receptor domain class A	PF00057		47.26	160	363
								76%	130	414
HFKHD91	1165344	73	blastx.14		(AF131842) Unknown [Homo sapiens]	gi 4406683 gb AAD20057.1		83%	79	150
HFKHD91	951259	145	HMMER 1.8		PFAM: EGF-like domain	PF00008		30.2	388	459
			blastx.2		Netrin-G1c.	sp BAB12008 BAB12008		52%	120	278
								60%	9	92
HUSXE73	1127979	74	blastx.14		(AF186111) NOTCH4-like protein [Homo sapiens]	gi 6014628 gb AAF01429.1 AF186111.1		28.84	119	211
								93%	2	286
HUSXE73	953246	146	HMMER 2.1.1		PFAM: EGF-like domain	PF00008		100%	360	863
			blastx.2		NOTCH4-LIKE PROTEIN.	sp Q9UHF1 Q9UHF1		95%	242	364
HNFCS26	899406	75	HMMER		PFAM: 7 transmembrane	PF00002		39.2	466	573
								100%	361	864
								65%	243	473
								249.7	146	853

HNFCS26	956682	147	2.1.1 blastx.2	receptor (Secretin family) (AC004262) R29368_2 [Homo sapiens]	gb AAC05172.1	81%	137	955
			blastx.2	(AC004262) R29368_2 [Homo sapiens]	gb AAC05172.1	80% 90% 52% 56%	324 169 208 143	554 324 267 190
HNFCS26	956684	149	HMMER 2.1.1	PFAM: Latrophilin/CL-1- like GPS domain	PF01825	23.7	1282	1151
			blastx.2	(AF114491) EGF-like module EMR2 [Homo sapiens]	gb AAF21974.1 AF1 14491_1	81% 48% 25% 31% 29% 70%	1109 75 159 132 153 1341	1978 419 1088 425 443 1370
HCE3H08	959861	76	HMMER 1.8	PFAM: Bacterial mutT protein	PF00293	33.27	273	392
			blastx.14	(AF062529) diphosphoinositol polyphosphate phosphohydrolase [Homo sapiens]	gi 3978224 gb AAC8 3224.1	73%	174	641
HETKR83	963274	150	HMMER 2.1.1	PFAM: EGF-like domain	PF00008	41.8	236	319
			blastx.2	Wnt inhibitory factor-1 - human	pir A59180 A59180	88% 35% 34%	20 20 29	445 325 319
HCUAZ04	965585	151	HMMER 2.1.1	PFAM: Fumarylacetoacetate (FAA) hydrolase family	PF01557	100.2	495	292

HCE3J83	968823	79	blastx.2	CGI-105 PROTEIN.	sp Q9Y3B0 Q9Y3B0	91%	546	214
			HMMER 1.8	PFAM: Bacterial muT protein	PF00293	6.52	356	385
HAPOI67	971184	80	blastx.14	(AF044588) protein regulating cytokinesis 1; PRC1 [Homo sapiens]	gi 2865521 gb AAC02688.1	98%	293	541
			HMMER 2.1.1	PFAM: 7 transmembrane receptor (Secretin family)	PF00002	280.3	1084	1842
HE8NI05	971303	152	blastx.2	(AF114491) EGF-like module EMR2 [Homo sapiens]	gb AAF21974.1 AF114491_1	52% 48% 70%	124 40 1307	1944 384 1336
			HMMER 1.8	PFAM: Low-density lipoprotein receptor domain class A	PF00057	59.46	307	417
HHENW06	971310	153	blastx.2	(AF166350) ST7 protein [Homo sapiens]	gb AAD44360.1 AF166350_1	97% 45% 48% 43% 52% 39%	106 193 283 632 579 118	597 411 411 766 653 186
			HMMER 2.1.1	PFAM: EGF-like domain	PF00008	35.6	852	965
			blastx.2	hypothetical protein DKFZp586M2123.1 - human (fragment)	pir T17298 T17298	98% 85% 38% 38% 85% 32% 39% 41%	17 840 786 32 488 870 798 840	334 1181 1106 331 583 1181 1085 1049

HNSMB24	971537	83	HMMER 1.8	PFAM: Trypsin	PF00089	40%	783	938
			blastx.2	MOSAIC SERINE PROTEASE EPITHELIALIN.				
HLMDO77	974855	84	HMMER 1.8	PFAM: Trypsin	PF00089	114.97	116	523
			blastx.2	Complement C1r-like proteinase precursor.				
HRDBE43	894862	85	HMMER 2.1.1	PFAM: Laminin G domain	PF00054	195.2	191	580
			blastx.2	CG8403 PROTEIN.				
HRDBE43	947966	155	HMMER 1.8	PFAM: Laminin G domain	PF00054	102.93	1023	661
			blastx.14	perlecan [Mus musculus]				
					gi 200296 gb AAA39 911.1	46%	963	640
						31%	1627	1250
						38%	1624	1361
						38%	1630	1379
						40%	966	715

HOGDR01	919899	86	HMMER 1.8	PFAM: Trypsin	PF00089	322.84	32%	957	661							
							72%	1696	1643							
							41%	1203	1132							
							47%	1840	1772							
							33%	1182	1111							
							50%	1242	1189							
							47%	1834	1784							
							45%	1867	1796							
							47%	1864	1814							
							57%	1182	1141							
							53%	1834	1796							
							61%	1020	982							
							44%	1194	1141							
							50%	1834	1793							
							63%	1828	1796							
							66%	1227	1201							
							53%	1834	1796							
							46%	1239	1201							
							47%	1188	1138							
							31%	1699	1643							
							40%	1538	1494							
							66%	1185	1159							
							54%	1828	1796							
							45%	1828	1796							
							60%	1227	1198							
							27%	1158	1060							
							42%	1023	982							
														322.84	171	881
														99%	165	890
														sp O43342 O43342		
							SP001LA (FRAGMENT). blastx.2									

HOGDR01	947085	156	HMMER 1.8	PFAM: Trypsin	PF00089	320.16	161	871
			blastx.2	(AC003965) SP001LA [Homo sapiens]				
					gb AAB93671.1	99%	155	967

[48] Table 2 further characterizes certain encoded polypeptides of the invention, by providing the results of comparisons to protein and protein family databases. The first column provides a unique clone identifier, "Clone ID NO:", corresponding to a cDNA clone disclosed in Table 1A. The second column provides the unique contig identifier, "Contig ID:" which allows correlation with the information in Table 1A. The third column provides the sequence identifier, "SEQ ID NO:", for the contig polynucleotide sequences. The fourth column provides the analysis method by which the homology/identity disclosed in the Table was determined. The fifth column provides a description of the PFAM/NR hit identified by each analysis. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, score/percent identity, provides a quality score or the percent identity, of the hit disclosed in column five. Comparisons were made between polypeptides encoded by polynucleotides of the invention and a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM"), as described below.

[49] The NR database, which comprises the NBRF PIR database, the NCBI GenPept database, and the SIB SwissProt and TrEMBL databases, was made non-redundant using the computer program nrdb2 (Warren Gish, Washington University in Saint Louis). Each of the polynucleotides shown in Table 1A, column 3 (e.g., SEQ ID NO:X or the 'Query' sequence) was used to search against the NR database. The computer program BLASTX was used to compare a 6-frame translation of the Query sequence to the NR database (for information about the BLASTX algorithm please see Altshul et al., J. Mol. Biol. 215:403-410 (1990); and Gish and States, Nat. Genet. 3:266-272 (1993). A description of the sequence that is most similar to the Query sequence (the highest scoring 'Subject') is shown in column five of Table 2 and the database accession number for that sequence is provided in column six. The highest scoring 'Subject' is reported in Table 2 if (a) the estimated probability that the match occurred by chance alone is less than $1.0e-07$, and (b) the match was not to a known repetitive element. BLASTX returns alignments of short polypeptide segments of the Query and Subject sequences which share a high degree of similarity; these segments are known as High-Scoring Segment Pairs or HSPs. Table 2 reports the degree of similarity between the Query and the Subject for each HSP as a percent identity in Column 7. The percent identity is determined by dividing the number of exact matches between the two aligned sequences in the HSP, dividing by the number of Query amino acids in the HSP

and multiplying by 100. The polynucleotides of SEQ ID NO:X which encode the polypeptide sequence that generates an HSP are delineated by columns 8 and 9 of Table 2.

[50] The PFAM database, PFAM version 2.1, (Sonnhammer et al., Nucl. Acids Res., 26:320-322, 1998)) consists of a series of multiple sequence alignments; one alignment for each protein family. Each multiple sequence alignment is converted into a probability model called a Hidden Markov Model, or HMM, that represents the position-specific variation among the sequences that make up the multiple sequence alignment (see, e.g., Durbin et al., *Biological sequence analysis: probabilistic models of proteins and nucleic acids*, Cambridge University Press, 1998 for the theory of HMMs). The program HMMER version 1.8 (Sean Eddy, Washington University in Saint Louis) was used to compare the predicted protein sequence for each Query sequence (SEQ ID NO:Y in Table 1A) to each of the HMMs derived from PFAM version 2.1. A HMM derived from PFAM version 2.1 was said to be a significant match to a polypeptide of the invention if the score returned by HMMER 1.8 was greater than 0.8 times the HMMER 1.8 score obtained with the most distantly related known member of that protein family. The description of the PFAM family which shares a significant match with a polypeptide of the invention is listed in column 5 of Table 2, and the database accession number of the PFAM hit is provided in column 6. Column 7 provides the score returned by HMMER version 1.8 for the alignment. Columns 8 and 9 delineate the polynucleotides of SEQ ID NO:X which encode the polypeptide sequence which show a significant match to a PFAM protein family.

[51] As mentioned, columns 8 and 9 in Table 2, "NT From" and "NT To", delineate the polynucleotides of "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth column. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the polynucleotides of SEQ ID NO:X delineated in columns 8 and 9 of Table 2. Also provided are polynucleotides encoding such proteins, and the complementary strand thereto.

[52] The nucleotide sequence SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, the nucleotide sequences of SEQ ID NO:X are useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in Clone ID NO:Z. These

probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to these polypeptides, or fragments thereof, and/or to the polypeptides encoded by the cDNA clones identified in, for example, Table 1A.

[53] Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

[54] Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and a predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing cDNA Clone ID NO:Z (deposited with the ATCC on October 5, 2000, and receiving ATCC designation numbers PTA 2574 and PTA 2575; deposited with the ATCC on January 5, 2001, and having depositor reference numbers TS-1, TS-2, AC-1, and AC-2; and/or as set forth, for example, in Table 1A, 6 and 7). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

[55] The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

RACE Protocol For Recovery of Full-Length Genes

[56] Partial cDNA clones can be made full-length by utilizing the rapid amplification of cDNA ends (RACE) procedure described in Frohman, M.A., et al., *Proc. Nat'l. Acad. Sci. USA*, 85:8998-9002 (1988). A cDNA clone missing either the 5' or 3' end can be reconstructed to include the absent base pairs extending to the translational start or stop codon, respectively. In some cases, cDNAs are missing the start codon of translation, therefor. The following briefly describes a modification of this original 5' RACE procedure. Poly A⁺ or total RNA is reverse transcribed with Superscript II (Gibco/BRL) and an antisense or complementary primer specific to the cDNA sequence. The primer is removed from the reaction with a Microcon Concentrator (Amicon). The first-strand cDNA is then tailed with dATP and terminal deoxynucleotide transferase (Gibco/BRL). Thus, an anchor sequence is produced which is needed for PCR amplification. The second strand is synthesized from the dA-tail in PCR buffer, Taq DNA polymerase (Perkin-Elmer Cetus), an oligo-dT primer containing three adjacent restriction sites (XhoI, Sall and ClaI) at the 5' end and a primer containing just these restriction sites. This double-stranded cDNA is PCR amplified for 40 cycles with the same primers as well as a nested cDNA-specific antisense primer. The PCR products are size-separated on an ethidium bromide-agarose gel and the region of gel containing cDNA products the predicted size of missing protein-coding DNA is removed. cDNA is purified from the agarose with the Magic PCR Prep kit (Promega), restriction digested with XhoI or Sall, and ligated to a plasmid such as pBluescript SKII (Stratagene) at XhoI and EcoRV sites. This DNA is transformed into bacteria and the plasmid clones sequenced to identify the correct protein-coding inserts. Correct 5' ends are confirmed by comparing this sequence with the putatively identified homologue and overlap with the partial cDNA clone. Similar methods known in the art and/or commercial kits are used to amplify and recover 3' ends.

[57] Several quality-controlled kits are commercially available for purchase. Similar reagents and methods to those above are supplied in kit form from Gibco/BRL for both 5' and 3' RACE for recovery of full length genes. A second kit is available from Clontech which is a modification of a related technique, SLIC (single-stranded ligation to single-stranded cDNA), developed by Dumas et al., *Nucleic Acids Res.*, 19:5227-32 (1991). The major differences in procedure are that the RNA is alkaline hydrolyzed after reverse transcription and RNA ligase is used to join a restriction site-containing anchor primer to

the first-strand cDNA. This obviates the necessity for the dA-tailing reaction which results in a polyT stretch that is difficult to sequence past.

[58] An alternative to generating 5' or 3' cDNA from RNA is to use cDNA library double-stranded DNA. An asymmetric PCR-amplified antisense cDNA strand is synthesized with an antisense cDNA-specific primer and a plasmid-anchored primer. These primers are removed and a symmetric PCR reaction is performed with a nested cDNA-specific antisense primer and the plasmid-anchored primer.

RNA Ligase Protocol For Generating The 5' or 3' End Sequences To Obtain Full Length Genes

[59] Once a gene of interest is identified, several methods are available for the identification of the 5' or 3' portions of the gene which may not be present in the original cDNA plasmid. These methods include, but are not limited to, filter probing, clone enrichment using specific probes and protocols similar and identical to 5' and 3' RACE. While the full length gene may be present in the library and can be identified by probing, a useful method for generating the 5' or 3' end is to use the existing sequence information from the original cDNA to generate the missing information. A method similar to 5' RACE is available for generating the missing 5' end of a desired full-length gene. (This method was published by Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)). Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcript and a primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest, is used to PCR amplify the 5' portion of the desired full length gene which may then be sequenced and used to generate the full length gene. This method starts with total RNA isolated from the desired source, poly A RNA may be used but is not a prerequisite for this procedure. The RNA preparation may then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase if used is then inactivated and the RNA is treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase. This modified RNA preparation can then be used as a template for first

strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis - reaction can then be used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant gene.

[60] The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC (deposited with the ATCC on October 5, 2000, and receiving ATCC designation numbers PTA 2574 and PTA 2575; deposited with the ATCC on January 5, 2001, and receiving ATCC designation numbers TS-1, TS-2, AC-1, and AC-2; and/or as set forth, for example, in Table 1A, Table 6, or Table 7) is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as described, for example, in Table 7. These deposits are referred to as "the deposits" herein. The tissues from which some of the clones were derived are listed in Table 7, and the vector in which the corresponding cDNA is contained is also indicated in Table 7. The deposited material includes cDNA clones corresponding to SEQ ID NO:X described, for example, in Table 1A (Clone ID NO:Z). A clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X, may include the entire coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Furthermore, although the sequence listing may in some instances list only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to sequence the DNA included in a clone contained in the ATCC Deposits by use of a sequence (or portion thereof) described in, for example Tables 1A or 2 by procedures hereinafter further described, and others apparent to those skilled in the art.

[61] Also provided in Table 7 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

[62] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Altling-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Altling-

Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

[63] Vectors pSport1, pCMVSPORT 1.0, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59- (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

[64] The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the deposited clone (Clone ID NO:Z). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

[65] Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X or the complement thereof, polypeptides encoded by genes corresponding to SEQ ID NO:X or the complement thereof, and/or the cDNA contained in Clone ID NO:Z; using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

[66] The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

[67] The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

[68] The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

[69] The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA sequence contained in Clone ID NO:Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X or a complement thereof, a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or the polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or a polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X,

a nucleic acid sequence encoding a polypeptide encoded by the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA contained in Clone ID NO:Z.

[70] Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in Table 1B column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in Table 1B column 6, or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[71] Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of,

sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[72] Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a

nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (See Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[73] Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of Table 1B column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1B column 6, or any combination thereof. In preferred embodiments, the polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1B column 6, wherein sequentially delineated sequences in the table (i.e. corresponding to those exons located closest to each other) are directly contiguous in a 5' to 3' orientation. In further embodiments, above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID

NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[74] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1B, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[75] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same Clone ID NO:Z. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[76] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same row of column 6 of Table 1B. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[77] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization

conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[78] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[79] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[80] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly

contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides, are also encompassed by the invention.

[81] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[82] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same Clone ID NO:Z (see Table 1B, column 1) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[83] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one sequence in column 6 corresponding to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) are directly contiguous. Nucleic acids which hybridize to

the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[84] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same row are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1B, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[85] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. Accordingly, for each contig sequence (SEQ ID NO:X) listed in the fourth column of Table 1A, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, b is an integer of 15 to the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. More specifically, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b,

where a and b are integers as defined in columns 4 and 5, respectively, of Table 3. In specific embodiments, the polynucleotides of the invention do not consist of at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. as disclosed in column 6 of Table 3 (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone). In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

TABLE 3

Clone ID NO: Z	SEQ ID NO: X	Contig ID:	EST Disclaimer		Accession #'s
			Range of a	Range of b	
HPLBY29	11	1041126	1 - 448	15 - 462	R33914, R33970, AA367795, and AA368685.
HOUEU57	12	1102662	1 - 453	15 - 467	
HNHFR39	13	1151373	1 - 778	15 - 792	AI917132, AW270385, AI061313, AA714011, AA582554, AL042373, AA644090, AA602906, AI278972, AA315361, AW338860, AI962030, AA630854, AA704393, AA833875, AA833896, AI309059, AA485328, AI310464, AI340151, AA904211, AA084609, AL037714, AA158549, T71936, AA622801, AA613761, AA484892, AA557911, AL135357, AA534064, AW057873, AI254779, AW194325, AA862183, AI031759, AI653776, AI792092, AI821056, AI821805, AI279037, AC007842, AC006512, AC005229, AC007227, AC003982, AC002351, AC004466, AC007637, AL049779, AC002091, AL022311, AL009181, AP000689, AC005412, AC007917, Z99716, U47924, AC007731, AC005500, AC003669, Z95152, AC007384, AL050318, AL034548, AP000355, AC006057, AL137100, AL022323, AC005874, AF134471, AC006511, AL022313, AC002301, AC004148, AC005030, Z85987, AL136295, AL008726, AL049709, AL109627, AC007312, AC005566, AF067844, AC003029, AL035423, AC002369, U85195, AC005962, AC006251, AC004832, AL021878, AC004520, AL132712, AE000658, AC005318, AC009247, AC005527, AC002430, AC007371, AC007537, Z82206, AL049759, AC000065, AL078477, AC004757, AC005694, AL117258, AP000692, AL034420, AC007686, AC005513,- U52112, AF064861, AC006530, AC002996, AC006211, AC007207, AP000030, AL079340, AC006449, Z85996, AC005529, AL021918, Z95114, AC005821, U91318, AL035405, AC002546, Z93242, AP000272, AJ229042, AC006312, AC007684, AL022476, AC005011, AL035422, AB003151, AC007551, AP000117, AF107885, AC002425, AC005952, U91321, AL031681, AP000557.

					AC005324, Z81369, AL049766, AP000251, AC005881, U80017, AL035555, AC004216, AC008545, AC007565, AC008134, AL133445, AC004975, AF001548, AC004067, AC003101, AC005071, AC004253, AP000104, AP000501, AC005031, AC004583, AP000697, AL049569, AL022316, AC005207, AL031118, AP000694, AP001053, AC006409, AC004686, AC005200, AC000025, Z83826, AC004922, Z93017, AL079295, AC004542, AC000353, AC001234, AC005592, AC004801, AL022312, AL031680, AL031848, AC002395, AF017104, AC005015, AC007011, AL133244, AC005370, AL049589, AC005225, AC004905, AC007216, AL034402, AC005519, AC003012, AC002310, Z95115, Z98304, AC000077, AC007421, AL031767, AL035667, AC004099, AP000031, AC002400, AC004526, U78027, AC004882, AP000505, AC005701, AL008627, AC005921, AC007055, AL031300, AL132987, AF196779, AC004647, AL022237, AC006333, Z97195, AC006958, AC007199, Z77249, Z93848, AC006077, AC006552, AL031295, AC008055, AL031228, AC007193, AL021154, L78833, AL022165, AC004382, AC005006, AL023807, AC004695, AC004996, AL022315, AC002115, AC006014, AF038458, AF222686, AC004962, AL109801, AF134726, AL133448, AC004551, AC005409, AC005736, AC007546, AL031589, AC005531, AL049839, AC005778, AL034549, AC004998, AL133245, AC005280, AC007057, AL021940, AL034429, Z98884, AC006441, AC006946, and AF111167.
HFATE17	14	1151475	1 - 626	15 - 640	AA777680, AA169599, AA034126, AA700597, AA203604, T48068, AA203588, AA705412, W90403, T51449, W90143, AW304561, AW302848, AA704530, and AC004542.
HNGER43	15	699391	1 - 302	15 - 316	AC007563, AC000030, AL023095, Z93928, AC002523, AC005035, AF043945, AL008634, and AC023328.
HWAAE95	16	1135294	1 - 1845	15 - 1859	AA468322, AW151541, T05834, AI865213, AI452836, AI370475, AI521525, AA533408, AW075979, AW117860, AA720582, AI921706, AL041375, AW020150, AA013168, AL041924, AL041381, AA747375, AA829065, AA019973, AA809125, AI078409, AI524453, AA449997,

					AA904275, AI358384, AA577706, AA493808, AA584489, AA084439, T51832, AI061313, AA365586, AA828047, AA720732, AW238712, AA584765, AA604843, AI280535, AI343143, AA526414, AI859834, AI251576, AA579398, AA642809, AA812058, AL042113, AI860423, AL044489, AA644090, AI800426, AI583466, AW271917, AA665645, AI754037, AA420723, AA665449, AA523812, H93293, AI801563, AI249688, Z98743, AL049869, AD000092, AP000301, AC004832, AC005899, Z83826, AL049694, AP000045, AF134471, AC006251, AL049589, AC005913, AL049843, AP000053, AP000168, AC007437, AL050348, AC006039, AC007386, AL031622, AC003109, AC002126, AC002416, AL109656, Z83846, Z98256, AL049766, AC005081, AC020663, AF111169, AC007350, U95743, AC004009, AF038458, AF196972, AL035610, Z93244, AC003098, AC007395, AL109733, AP000121, AC009181, AC005755, AB014078, AC004263, AC007537, AC005754, AL031281, AC008123, AC004967, AC005666, AL031722, AP000514, AC005529, AC007193, AC002544, AL078581, AC002316, AC006312, AL035420, AC005516, AC004087, AL031297, Z95331, AC003035, AC009247, AP000113, AC003042, AL022721, AP000326, AC005527, AC006139, AP000169, AP000122, AP000054, AC006057, Z98200, AC005180, AC002347, X55448, AC004743, AC003956, AL034351, AP000065, AC000134, AL133448, Z99754, AC004817, Z82190, AC004464, AC004022, AC000120, AC007993, AL049709, AC008101, AL121576, AP000692, AP000152, AC004382, AL117340, AJ011712, AC000075, AC005006, AP000512, AC004383, AF045555, AC006241, AC003101, AC007637, AL133485, AC002381, AC005255, AL080243, AC005004, AC004752, AC004874, AL008631, AF134726, L78833, AP000300, AL049871, Y10196, AP000502, AL109627, AC007225, AC004984, AL022323, AC004841, AP000555, AC005164, AB015355, AC004799, AC002094, AC004755, Z49237, AC003043, AL023803, AC005318,
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HMSGL27	17	638097	1 - 1599	15 - 1613	AA287567, AA252404, AW249468, AA547979, AA601218, AA287570, AA569648, AA255853, AI986165, C18751, AA505108, AA126763, AI732430, AI732458, AA127499, AA984187, AA814400, AI917132, AA714224, AA758277, AA085372, AI380617, AI669421, AA714110, AI040051, AL041894, AA610432, AI912401, AW021917, H80203, AI623764, AI923052, AI821044, AI354423, AA515728, AI679413, AI061313, AA604645, AA528390, AW270258, AA582554, AL079734, N32944, AA652868, AI206841, AI783911, AA569667, AA745653, AI962030, AA410788, AI733856, AI244127, AL040054, AW271917, AA579179, AI499954, AI569086, AI862716, AW020088, AI620585, AI885488, AI078409, AA584066, AI561060, AA284247, AL120343,

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HKIXB77	18	1161224	1 - 1222	15 - 1236	AI674873, AW023532, W17106, AI963720, AI334443, AI284640, AI305547, AL138265, AI249997, AL046409, AL041690, AI431303, AI305766, AW303196, AW274349, AW193265, AW301350, AL119691, AI754955, AL046205, AA521323, AI110770, AI345518, AI076616, AW327868, AL120687, AI270117, AA610491, AW419262, AI345654, AA126450, AW265393, AA521399, AI312309, AI281881, AW265385, AI064864, AI613280, AW270270, AI969436, AI133164, AA665330, AW028429, AL045053, AL138455, AA581903, AI754253, AA587604, AI798473, AI610159, AL120269, AL037683, AI801591, AI696962, AL046457, AL044940, AI053672, AI537506, AI350211, AA490183, AI732865, AL040921, AI754658, AL042853, AL039958, AW238278, AL042753, AW088846, AL079645, AL134972, AA720702, AW439558, AA680243, AI473943, AW276827.

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HTNBM01	19	1207944	1 - 2888	15 - 2902	N76151, N98639, N95698, N98646, AA298841, Z28624, N54699, and AW383079.
HBJGT92	20	1193035	1 - 1851	15 - 1865	AI904002, AA469156, AA579296, T84928, AA613878, AI690474, AL037285, AA548492, AA133651, F18394, AA347830, AA279319, F18776, F31465, AA650183, AA133650, R91633, T06876, AA661554, AI752977, AF196972, AL035405, AL031680, AC005859, AF196779, AL035555, AC002456, AC004851, AL049589, AL132774, AC005815, AC007285, U91318, and AC007637.
HAGAT56	21	1218696	1 - 2004	15 - 2018	AI014830, AA683268, AA403131, and AW772256.
HCFMG57	22	1205913	1 - 2478	15 - 2492	AW378455, AW378475, AA865755, N32743, AI627210, AA521490, AI863026, AI475665, AI090241, AI131107, AI686842, AI955157, AI762812, AI953913, N34451, AW205599, AI809165, AA912720, AI693617, AA810228, AI817219, AI695046, AI381457, AW274030, AI521150, AI141883, AA742507, T08123, AA740430, H09272, AI968969, AI572995, AA283075, AA347459, AA832491, AI434727, AI270742, AI610832, AA836638, H85723, T58842, AA134255, T58825, T34522, AI983553, H09273, AA347458, AA835719, N55725, AA296687, AA134254, H85213, AI351833, N42860, N92942, AW103718, AA774947, AI276440, AW007262, AA514997, AA654384, R57698, AW351892, U95740, and AB007890.
HTEHS55	23	1195572	1 - 1162	15 - 1176	AI669827, AI675110, AI916264, AI022830, AI003782, AA404248, AA404272, AI480396, AI819299,

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HMUBI13	24	1189811	1 - 1334	15 - 1348	AI341467, AI279873, AI815782, AI608966, AW162570, AW161752, AI357796, AW160967, AW303833, AA211700, AI081095, AI083998, AI309740, AI866956, AI083946, AW161216, AA428187, N26682, N39835, AA431956, AA428676, AI815401, H09215, H09158, AA928901, AA779040, AW243698, AA053174, AI363969, AI284640, AL046409, AI281881, AI431303, AW193265, AI679782, AI334443, AW301350, AW303196, AW274349, AI270117, AL041690, AI613280, AI110770, AI064864, AI345654, AW088202, AI631232, AL038785, AI963720, AL037683, AW419262, AW029038, AI017024, AI537506, AA490183, AA720702, AI457397, AW270270, AW406447, AW162049, AI962050, AI929531, AW088616, AW021583, AI339850, AA610491, F36273, AI754658, AL044940, AI570261, AA482711, AI904894, AA587604, AI471481, AI133164, AI625244, AW073470, AI754955, AI061334, AI349850, AI281697, AL138455, AI307201, F08612, AW238278, AW088846, AW193432, AA521323, AI688846, AI281903, AL120687, AI917271, AI918421, AI567674, AA857486, AI192631, AI286356, AW261871, AI350211, AW166815, AL119691, AA522942, AW072587, AA613227, AA713815, AL119984, AI446464, AW275719, AW302450, AW148792, AW079659, AW440836, AI732865, AI049722, AI251436,

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HPCAO89	25	1137858	1 - 1525	15 - 1539	AI391500.
HE2KN09	26	1163877	1 - 1357	15 - 1371	AW409694, AW163484, AA524968, AW157422, AW409789, AW149826, AW439315, AI435067, AW082947, AI982972, AA855083, AW027529, AI081884, AW083431, AI004310, AI748899, AI188316, AI355876, AI302238, AI275061, AI459896, AA961666, AI139136, AI418038, AI079833, AI278587, AA488886, AA865815, AA865641, AW192032, AA708607, AI863272, AI420439, AI936078, AA662188, AI826981, AI140216, AA704357, AA662145, AI803886, R60985, AI199200, AI199350, AI202396, AA987295, AA085191,

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HCWGE12	27	1171961	1 - 517	15 - 531	
HCEPY32	28	1199930	1 - 2613	15 - 2627	AA326530, AI590906, AA197019, AI284126, AL040054, T74524, AA640685, H73550, AI887235, AW304580, AI188522, AA643770, AI358712, AL038842, AI669589, AI306232, AA904211, AA578621, AA502532, AI284640, AA584862, AA127426, AI278972, AW274191, H29914, AA056248, AI962030, AW029515, AW103758, H05066, AA847427, AW302711, AA323644, AA533054, AA661573, AA847508, AA493226, AI798407, AI439393, AW275971, AI802087, AI633168, AA302812, AI675615, AI251576, AI144081, AW338508, AI961983, AA825827, AA502991, AA525293, AI417469, AI732690, AA595499, AI431513, AI499954, AI369580, AW302753, AW238253, AI245693, AA827383, AA503298, AA765925, AL120282, AI801505, AI635440, AA577755, AW150077, AA602906, AI523316, AA613761, AW303872, AA302971, AA775205, AA070899, AI984168, AW410784, AI583466, AW167330, AI823705, AI335995, AI824476, AA832175, AI568849, AW440368, N23913, AI076228, H07953, AA713705, AA663074, AL079734, AI277454, AI251696, AI049709, H63660, AI753672, AA832444, AI334896, AA515728, AA381138, AA719433, AI732710, AI732677, AI358343, AI005613, R98218, AI367473, AI732869, AA634786, AI889245, AA993636, AI925065, AA491814, AI205181, AI246996, AL137536, AC006512, AL008583, AC005971, AC000353, AC002980, AL031295, AC002300, AC002097, AC005512, AF111168, AL021397, AL133448, AL034374, AC004967, AL023575, Z93023, AL031846, AP000208, AP000130, AL109984, AL034420, AC002316, AL033527, AC005754, AL035652, AC004774, AC011625, U89335.

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HSVCH37	29	1081035	1 - 236	15 - 250	AB001632, I58533, I58528, AB015656, I58538, AJ004865, AF043731, D89094, L16545, and I58526.
HOFNL18	30	1204713	1 - 1676	15 - 1690	AW079905, W72340, AI827569, N21556, AI669118, AW103945, AA495817, AA477583, AA495757, H15484, AI245484, AI921696, AI922971, AI561233, AA304945, AI654287, AA558780, R56490, AA357914, AA628687, AA355289, AA477457, AA832308, N79824, C14941, W73971, AI434108, AA806856, N41499, AA781710, AI372958, AA312114, AA341504, AI093765, AA341300, H57022, AA099228, AW450650, N40267, AW451773, AW236015, AW390225, AA385861, T10380, AA098883, AL080166, and AL031432.
HTOCG37	31	1189012	1 - 1349	15 - 1363	AI884975, AW088080, AW246654, AW204224, AW138277, AA772919, AI366161, AA558898, AI381656, R40390, H17482, AA233993, Z17368, R45475, AI871516, AA513619, AA190710, AA191531, AA385883, AA280111, AA669493, AI740693, AL133979, AA626586, AI199985, AW361314, AA281756, AA860184, AI969999, AF079529, AF056490, AR025390, AL109778, AR025391, and AL109687.
HTEOF80	32	1143414	1 - 1712	15 - 1726	R99817, AF186084, and AL117610.
HSLDP32	33	1182295	1 - 620	15 - 634	
HAICQ62	34	1182256	1 - 1169	15 - 1183	AI814314, AW361172, AW368430, AW368437, AI819230, AW361245, AI828999, AW361164, and AW368433.
HRDBE43	35	894862	1 - 1868	15 - 1882	AI160324, AA420500, AW263972, AI206613, AI417744, AI953056, AA778217, AI863306, AI804393, AI432712, AI587218, AI218649, AI339726, AA780366, AI825578, H70209, AA470738, AI669249, H70546, AI611674, AI792038, R08140, T82124, AI791228, AI820643, AA847657, AI342131, AI342141, AA989292,

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HSSKD85	36	908141	1 - 1136	15 - 1150	AW024960, AI479960, AI052585, AI139986, AA135576, AW137104, AW205456, N30762, AI631818, AI187156, AA830014, AI452434, AA634216, AW088488, AA398256, AI859053, AI088449, AI159823, AA564062, AI494095, AA158516, AI311717, AA811798, AA226160, AI873741, N25872, AA146624, AA761003, AA190958, AI066392, AA535733, AI278434, W92242, AA225625, N40580, H94758, AI382438, AI796467, W92243, R59937, H94384, H94363, AI969940, W70120, AW338143, W99328, AA143555, AA399431, AA190865, N45043, AI718153, AI245054, AI906964, AI760352, AA135514, AA653523, AI708811, AA034276, W69970, AA156400, M93661, D32210, and U57368.
HCRMV17	37	1180333	1 - 1474	15 - 1488	AI492198, W44823, W39773, AL044584, AA381672, AB002357, and D26077.
HFOX77	38	1137799	1 - 767	15 - 781	W22070, AB033063, and AR065869.
HBXCZ29	39	1226989	1 - 2442	15 - 2456	AA298841, Z28624, N95698, N98646, N98639, and N76151.
HRDBJ38	40	1227194	1 - 1774	15 - 1788	AI828007, AI075340, AI338572, AI683815, AI338134, H29723, AI221309, AI348269, AA774440, AW072554, R72306, H29724, R82932, AA447906, R83115, AA661652, AI932413, R72359, C03492, AA936172, AA451938, C15076, D59467, D80164, D59502, D51423, D81026, C14389, D59275, D59787, D80038, D80195, D59610, D80193, D81030, D80227, D58283, D59859, D80022, D80166, D80253, D59619, D80210, D51799, D80391, D80240, D80043, D80269, D80241, D80212, D50979, D80196, D80188, D80219, D57483, D59927, C14331, D80366, D59889, D50995, AW387762, D80251, D80024, D52291, D51022, D80378, AW177440, AA305409, D80045, C14429, AA305578, AW378532, T03269, D80522, AW178893, D51060, C75259, C14014, AW179328, AA514188, D80248, D51250, T11417, AW369651, AW352158, D80134, AW178762, D58253, AW178775, AW177501, AW177511, AA514186, D80133, C14077, AW176467, AW360811, AW352117, C05695, F13647, AW377671, AW375405, D80268, AW378540, AI910186, AI557751, AW366296, AW360844, C14407, AW360817, AW375406, AW378534,

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HCOKA10	41	907080	1 - 759	15 - 773	AW327294, F31091, AA528669, AA505384, AW328419, AW328418, AW419243, AA187998, AA640483, F31092, AA420717, AI348852, W81029, AA482925, AI879569, AA946918, AA314600, AA825612, AA808869, W45176, AA316648, AA651658, AI735276, W52650, AA534263, AA314556, AA417254, AI342431, AA622408, AA181138, AA506547,

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HKGDI91	42	1137801	1 - 1156	15 - 1170	AI952995, AW071872, AW297176, AW131657, AI871511, AI568544, AI341664, AA833875, AA833896, AW276827, AI884982, AL046409, AI362442, AI887085, AI356440, AI687343, AI133083, R64640, AI613280, F36273, AI627917, AW073510, AI688846, AI431303, AI612142, AW338086, AI521525, AI375710, AI214075, W60522, AI921765, AW193432, AI284640, AW020150, AI281881, H88666, AW238278, AW341903, AW166611, AI433131, AI246796, AI345654, AI610941, AI270117, AI471481, AI537368, AI926102, AA669840, AI224583, AI866970, AW406162, AA601336,

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HLCMP75	44	1203728	1 - 1551	15 - 1565	AA595199, AA430329, AI339553, AI041943, AI284951, AA730621,

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HWHQR25	45	1126358	1 - 710	15 - 724	
HLKAB61	46	1183217	1 - 519	15 - 533	AW024960, AI479960, AI052585, AW205456, AA830014, AA398256, AW137104, AI859053, AI873741, AI796467, AA225625, AI159823, AA811798, AI718153, N25872, AI969940, AI382438, AI311717, AW088488, AI187156, AI278434, AI088449, W92243, AA761003, AI631818, AA146624, AI494095, AI452434, AI066392, AI245054, AA535733, AA190865, R59937, AA158516, N30762, AA634216, AA564062, AI139986, AA135576, W70120, W99328, AA399431, AA226160, N45043, AA143555, AI906964, AA190958, AA034276, AI708811, W69970, N40580, H94758, AW338143, and M93661.
HEGAZ61	47	1226372	1 - 2397	15 - 2411	AL046428, AI208246, AA724983, AI221180, AI689614, AA514684, AI434656, AI583578, AW088944, AL110306, AI929108, AW161098, AI570966, AW262042, AI925463, AI687568, AW148478, AI802240, AI365256, AI760991, AW265004, AW074702, AW089932, AI689470, AI348777, AW131112, AI699011, AI272973, AW089006, AI824497, AW081343, AI953765, AI335426, AW088899, AW074605, AI537617, AW188438, AW130849, AI432570, AW085786, AL046463, AA455772, AI621341, AI249946, AI591407, AI277008, AI539153, AI659795, AI419650, AI457490, AI524179, AI865297, AI419440, AI434242, AI866608, AI446124, AA830821, AI633419, AI921746, AI648502, AI500514, AI472536, AW028442, AW149069, AI873704, AW074374, AI266719, AI537190, AA999906, AW149876, AI873638, AI886055, AW411008, AW088131, AI631977, AI274500, AI801602, AI698437, AI677797, AI932739, AI866111, AI678762, AL041150, AI567302, AI857296, AI185535, AI366922, AI254754, AI141288, AW083149,

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HPJEQ52	48	1216564	1 - 2006	15 - 2020	AI963029, AA737799, AA622208, H54262, AI687468, AI819928, AW002750, AI863520, AI669204, AI910600, AI350437, AW015174, AA513377, AW149964, H54263, AW338035, AW338021, AA706495, AA536040, AI755214, AI754567, AA773463, AA515048, AA410788, AI754105, AW075729, AW272294, AI923052, AA643770, AI755057,

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HFIZB56	49	1137798	1 - 1878	15 - 1892	AW410354, AI358384, AA584489, AI040051, AA644090, AI696793, AA720732, AA169245, AW021583, AI587583, AA630672, AI587565, AA574442, AA491284, AI282479, AI623764, AI254779, AW020094, AA993818, AW302909, AI796627, AW021399, AI205181, AI754037, AI732120, AI491867, AA680243, AA610509, AA634786, AI580652, Z98200, AL034343, AF001548, AC008372, AC005765, AL021154, AP000261, AC006141, AC005086.

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HTTKB18	53	963346	1 - 2734	15 - 2748	AI961227, AI749275, AA403194, AI830546, AA401204, AI571463, W93852, AW274921, AW073425, N30125, AA620397, AI686865, AI889248, AA126464, H97568, AI185855, AA307735, AL041718, AL043648, AA620415, AI590372, AA191661, AA633723, AA704011, AW161618, AW088454, AI636656, AL043647, AW081564, AA406165, AI493560, AA526893, AW238853, AA635393, AI240253, AA653896, AI280716, AA634345, AA744797, AW362551, AI351127, AA831120, AA976285, AA568447, AI263591, AA179982, AA600055, AL048887, AI168077, AL041719, W19227, AI245315, AI289860, AA191045, W05431, AA031816, R14188, AI289422, AW151225, N70561, AA702301, AA888823, AA082994, N49248, AL041076, AA031817, AA251519, N30446, W56368, N86136, AI440100, AI159966, AI637813, W24380, AA435640, T62855, AI459439, AI524301, AA714535, W56579, N36319, N29982, AI719670, T57671, AW052052, N26528, H39930, AL039920, AI708274, AW135147, AI523470, R13695, AI206212, AA055212, W44915, W31591, AA329330, AW004674, W32329, H60068, R37791, AA541333, H13593, AI557672, AW003494, AW082439, H59412, AI272822, N42359, T91235, W15519, AA121016, T34649, W24756, AA299018, AA350109, R15057, AA856703, R86309, T33241, AA083151, T36199, N35736, T16413, AA031795, R12004, N56051, AI557677, AI557674, AI867852, AW007106, H00125, T75430,

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HPTZB93	54	1222478	1 - 1052	15 - 1066	AW138281, AW206040, AI279486, AI817720, AW205987, AW206016, AI694554, AA862263, AI860959, AI298729, AI299747, AI216051, AW340960, AI703067, AI885693, AW341220, AI681397, AI802146, AI066735, AI279331, AI298540, AI912139, AI630777, AI127856, AI634502, AI268259, AI796940, AI129532, AI299414, AA923300, AI692842, AW140104, AW137441, AW207254, AI216530, AI914342, AI268955, AI459037, AW136174, AI299132, AA938376, AI693815, AI912208, AI301061, AI002211, AI299900, AI298698, AI298009, AI702631, AI871768, AI810454, AI689870, AW016202, AI458645, AI222004, AI689871, AW102711, AI702711, AI732920, AI732919, AI689859, AI804311, AA995350, N68345, AI351290, AA962534, AA825171, AA878309, AI476744, AA974790, AA934499, AA528135, AI702851, AW024083, N94016, AI187311, AW003096, AW003320, AI670694, AI223259, AW139377, AA916697, AI791238, D50979, D59859, D80022, D59787, D80166, D80253, D80024, D80391, D57483, D59275, D80196, D80366, C14429, D51423, D81030, D59889, D58283, D59619, D80210, D51799, D50995, D80240, D80195, D80188, D80212, D80043, D80219, D80164, D80227, D59927, D80269, D80038, C14331, D80193,

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HELDY60	56	1056195	1 - 3709	15 - 3723	AW368397, AI679767, AI298034, AI681770, T86312, AA332746, AA379823, AA135903, D62730, and T93939.
HNALE30	57	1219068	1 - 1915	15 - 1929	AL043399, AL043397, R36317, R60363, AA229782, W19800, Z44585, T84431, R73933, W19896, W68673, AA229886, AA781657, R25660, AW407804, R15164, W45109, AA724662, D83778, and U63963.
HWADY16	58	1182316	1 - 993	15 - 1007	AI245977, AI739455, AI418285, AI739445, AI992157, AW453013, AI333190, AI369184, AI539630, AI278907, AI276810, AW028204, AI241009, AA143160, AA283147, AI739368, AI198469, AI246744, AW296566, N39722, N28707, AA765166, AI682209, AA142881, AA232819, AI498387, AA233873, AC007785, and AW469104.
HNTRU73	59	1173875	1 - 516	15 - 530	AI492198, W44823, AA381672, AB002357, and D26077.
HLHCR16	60	910123	1 - 3790	15 - 3804	AA402528, AI379350, AA716107, AI123557, AI127175, AA234106, AA234698, AI039768, N77999, AI580137, AA424560, AA419490, AI334141, R71349, AI224976, AI417798, AI080508, N58410, AI818475,

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HFJKO15	61	910828	1 - 526	15 - 540	AI148246, AW241903, AA234558, AC007731, AC005500, AC000096, AC007731, AC007731, AC005500, and AC005500.
HMEIS32	62	1164006	1 - 1722	15 - 1736	AL039245, AI955098, AI857804, AI355557, AI469403, AW249170, AW167089, AW264538, AI922792, AI090862, AA614415, AW015755, AI589853, AI970459, AW264730, AW302158, AI591130, AI990223, AI860824, AW248743, AA954810, AI652051, AI634311, AI739259, AI886436, AW196771, AW078970, AA908313, AI798561, AI611669, AA506437, AW079611, AI912359, AA131747, F37324, AW183471, W19261, F27752, AW339361, AA679753, AA514635, AA962100, AA330885, H91413, AI869375, AI829609, AW297389, AA465711, AW050424, AA131835, AA355811, AI587515, AA583508, AI583202, and D63481.
HOGDR01	63	1133383	1 - 1425	15 - 1439	AI805425, AW273749, AA884001, AW276210, AW317074, AW295870, AW383315, AW152554, AI940071, AI969215, AW383305, AW383297, AW083601, AI249364, AI566393, AI739044, AI357916, AI671350, AW304326, AW079920, AW083723, AI274014, AW392670, AL119324, AL119399, AL134527, AW384394, AW363220, U46351, AL119443, U46347, AL119522, AW372827, Z99396, AL119319, AL042544, AL119457, AL119418, AL134902, U46350, AL119439, U46349, AL119484, AL119391, AL043003, AL119483, AL119497, AL119401, AL119363,

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HISBG28	64	1180262	1 - 2717	15 - 2731	AJ810118, AA909711, AA481627, AW104339, AA651933, AJ016329, AJ075273, AA992565, AA927147, AA829327, AA766107, AA805533, AJ002215, AA808082, AA883142, AW027440, AA705065, AA811592, AA490829, AA765432, AI636538, AA648823, AA868183, AA719942, AA904820, H65033, AI884514, AI185534, AA732713, AW376426, AA766740, AI888635, AW292729, H65034, I22485, L12052, U67932, U68171, and U77880.
HBJIG82	65	1151379	1 - 581	15 - 595	AW161406, W22101, AW081698, AA976942, AI349772, AI499463, AW135090, AL121270, AL135661, AI633419, AW268253, AL045500, AW071349, AL036146, AI312428, AL036802, AW104724, AI868831, AI684265, AL036396, AI433157, AI064830, AI349645, AI500077, AL047763, AI580190, AI433976, AI436456, AL047042, AL120854, AW302965, AA613907, AW162071, AL119049, AL119748, AI682743, AL119791, AA640779, AW002342, AI590120, AL040169, AI439717, AI345735, AI469532, AI906328, AI567351, AI207510, AI699857, AW238730, AI349614, AI349598, AI610645, AI349933, AI538716, AA987764, AI282903, AL046849, AI568870, AI500553, AI340582, AI920968, AW132034, AW166645, AI678302, AW118512, AI521012, AI570384, AI349004, AL036274, AI273142, AL120736, AI269696, AW268220, AI815383, AI648684, AI873731, AW074993, AW080838, AW103371, AW087445, AI687376, AA326433, AI569616, AL036759, AI312152, AW117882, AW131954, AW301409, AI907070, AI349937, AW089572, AI334884, AL045266, AI702406, AI863014, AI249257, AI952360, AI636445, AI273048, AW196141, AI612920, AI554484,

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HBMXS88	66	1162642	1 - 1606	15 - 1620	AI949632, AI354431, AI651157, AW386234, AA236937, AI582330, AW138858, W58355, AI051321, AA455638, AI819589, AA780023, AI040449, AA237086, AI579904, AA815150, AI989896, W90300, AA582235, AI076754, AA455691, AI086973, R51088, W90641, AI079206, AI363297, R89165, AA705343, AA676557, AA025508, AW393458, AI005395, AI312921, AA701484, AA973550, AW075301, AI697773, AA810053, AA045824, AA806111, AI204604, AA295260, AA045939, AI767182, AA902496, AA295048, R35520, AI701757, AW050442, N47376, AA613051, AI419623, AA317608, AA025911, AA779479, AF151811, L38481, and Z98752.
HE8UL90	67	1226071	1 - 2743	15 - 2757	AF154671.
HWHGF95	68	1152274	1 - 1361	15 - 1375	AA583908, AF135026, and AB012761.
HNKAZ51	69	1152347	1 - 910	15 - 924	U77054.
HFKKE19	70	1127465	1 - 740	15 - 754	AI866028, D87469, and AL031597.
HILBH66	71	1048931	1 - 676	15 - 690	AW271361, AI669661, AI066605, AA425588, AI735664, AA195146, W74608, AW027978, AI018730, AI935510, AI185633, AW043919, AA993404, AI640585, AI927620, AW002498, AI934436, AI559981, AI968681, AI672299, AI422678, AA569942, AI378894, AI659268, AI273512, AI436227, AI363301, AA766347, AI380745, AI206984, W94646, AA773648, AI094063, AA628526, AA989426, AA889351, AA883824, AW002369, AI355683, AI373924, AI817823, AI763339, AI278238, AI767047, AA889352, AI127585, AI360752, AA195282, AI971450, AI132981, AI962756, AA902222, AI767875, W94385, AA569949, AI468466, AI240574, AI190556, AW013937, AI240575, AW104888, W94608, AW268725, AI133092, H79051, AI140477, AI366169, AA425451, T28917, D59520, AA657883, AI202549, AI205492, AI916042, AI695700, AI184045, AW104299, AA503512, AI648700, AI743100, AI824883, AI652636, AA091770, AI982950, AA994143, AI383570, AA918387, AW298255, N40872, AW204184, AI355665, AA748371, N30085, L25851, I33984, AF020046, U12236, AF020045, AW510360, and AW591932.

HWMEQ37	72	1226808	1 - 1781	15 - 1795	AI924527, AI924182, AI597567, AI368169, AA143746, AA143761, AW292063, AA126071, D31382, AW177469, AA056638, AI056960, AI084845, AW177487, T79589, U54603, AW352026, AW365560, AI927431, AA641005, AI762083, AI380837, AW177675, AW271159, AW178439, AI587618, AF216312, E13203, and AW613143.
HFKHD91	73	1165344	1 - 1355	15 - 1369	AI858128, AA422028, W74456, AI524577, W79191, and AB023193.
HUSXE73	74	1127979	1 - 1295	15 - 1309	AW138763, AI968244, AI671228, AI146849, AI650986, AA974891, AI935406, AI375139, AI632343, AI580312, AI190358, AI823383, AA758662, AW166381, AI816934, AI362170, AI307616, AI339511, AI092493, AI193719, AA676785, AA701414, AI375073, AI090245, AI077483, AW003931, N70081, AI307365, AI991601, AI967935, AI990350, AI637874, AI825545, AI621021, W67234, AI186726, AW206481, N30322, AW140070, AW338117, AA031644, AI095704, H00954, AI859068, AW136394, AW263085, R39467, AI984849, AW338430, AI219050, AI334231, R62632, AI241351, AI355851, AI334036, AA449686, AI336416, H72039, AI735518, AA699736, R39468, F26300, R30863, AI130689, W67345, AI620138, AA358091, N74688, AA704504, AI524317, AI183860, AI801924, R74316, AI933476, AI933484, AA448958, H16951, N56653, R62685, AI634964, AA031725, H72038, T19026, AI433512, H00953, R31133, AW192226, AW235028, AI888621, AW190428, AI805638, AW029072, AI539153, AI628292, AI921082, AI379711, AW029606, AW188491, AI583533, AW002174, AI091468, AI598113, AI636719, AI358455, AI620093, AI566507, AI498579, AW168723, AI811192, AI207454, AW088899, AI366549, AL046463, AI866608, AI874410, AI611743, AW083804, AW118332, AA830821, AI696626, AI589993, AI365256, AW085786, AI805769, AW265004, AI677797, AI364788, AI648567, AW089801, AI636619, AI866786, AW051107, AI866082, N74355, AI282651, AW129271, AI863397, AI310155, AI952920, AI536557, AW172723, AA579232, AW403717, AI539771.

					AW131954, AA420722, AI919345, AI805688, AI251830, AI565125, AI862324, AA807352, AW168373, R40432, AI539632, AI470701, AI738867, AI312428, AI434242, AI371228, AI801605, AW080080, AI610429, AW168425, AI432736, AI307736, AI473598, AI499986, AI273839, AA928539, AI872064, AI568870, AI868831, AI869750, W33163, AI874151, AI950664, AI436429, AW087901, AI470293, AI570966, AI867042, AW082040, AI929108, AI537837, AI573026, AI699862, AI859464, AI242646, W46547, AI445430, AI249877, AI862144, AI689420, AI879693, AI249946, AW130863, AI922577, AA848053, AW059713, AW068845, AI345677, AI274769, AI554218, AW192375, AA572758, AI872051, AI375730, AW161892, AI800152, AW191844, AI917055, AW151750, AI702301, AW088134, AI500146, AI699255, AI570384, AI633477, AI680498, AA176980, AI453413, AI370390, AL047344, AI499512, AW162194, AI889147, AI678411, AI636445, AI494201, AI561299, AA693347, N71180, AI686823, AI539071, AI537307, AI674838, AA761557, AI344935, AI886124, AI476077, N75771, AI885974, AL036718, AI872074, AI560010, AI537617, AI311892, AI623682, AF186111, AR059958, AL137556, AL122121, AL136842, AL133093, AL122111, AL080127, A08910, A08909, A08908, I41145, E15324, AJ242859, AF113676, A08916, AL133645, I00734, A18777, AR019470, E00617, E00717, E00778, AL035458, I89947, I48978, A08913, I89931, AL133077, AF090896, I49625, A08912, AR038854, AB019565, AF093119, AL133104, X62580, I26207, AL137527, AF000145, AL080060, X52128, AL080158, AF051325, E08631, D44497, AC002467, X53587, AF119337, A90832, AF097996, X70685, AL133075, AL080137, AL133031, AL122123, AL137300, AF012536, L13297, X92070, A23630, AL133081, AL117585, AF004162, U72620, AL122050, AL137281, AL137648, U96683, AL133568, AF085809, AL133080, AL122098, AF125949, AL137273, X93495, AF081197, AF081195, I89934, I89944, M86826, AL133067, I09360, I33392, AL049466, I68732, AL137665,
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					S68736, AL080086, AF003737, AF110329, Z72491, AF106827, L30117, U55017, AF017152, AF090886, AL133014, A12297, AL133072, X65873, AJ006417, E15569, AL049465, AL137429, E03348, AF031903, AL137557, AL137258, U68233, I92592, E07108, AF158248, AL122118, AL110222, U91329, S76508, AL137479, X72889, AF113691, AL137463, S61953, AL122049, AF118064, AF118070, AJ000937, AL133098, AJ238278, D89079, AL133557, I30339, I30334, Y09972, U49434, U80742, AL137705, AL133113, AF026816, AL117432, X81464, AF111112, AF162270, U00763, AL137283, AL049938, AL049283, U67958, AL049382, I42402, AF111851, AF210052, I17767, AF159148, AL137538, AL137529, AL117457, S77771, AL096744, AJ003118, AL050146, AF106862, AF067790, Y10655, Y10080, E02253, Y10936, AR000496, U39656, AR038969, A49139, Z37987, U00686, AF040751, AL050108, S79832, AF022363, M92439, AL110218, A93016, AF113013, L04849, A08907, AF078844, AF091084, AL137526, X87582, E05822, AF132676, AF061836, AL117583, X67688, X84990, E06788, E06790, E06789, I09499, A45787, I66342, AL137294, AL050138, AL122110, AL137574, AL050277, E04233, AL110196, AL049314, AF079763, A07647, AL137712, U68387, AL110225, AL117394, AF069506, AL050393, U42766, AL133565, AL133606, X63574, AF061573, AF057300, AF057299, U88966, AF142672, A21103, AL110197, AF028823, AF100931, AF113689, AF126247, L19437, Y11587, AL137478, AL080159, AL137640, AL133640, AB007812, AF061795, Y14314, AF151685, AL133016, AL117440, AF061981, U78525, AL080148, AF030513, and I48979.
HNFC26	75	899406	1 - 1687	15 - 1701	H70763, AW376414, AW403498, AW205281, AW204171, AW450761, AI571894, AF114491, AC004262, AC005327, AC004999, AF053356, AC004841, AL021707, AC003010, AC004834, AC007151, M22403, AC007663, and AL034400.
HCE3H08	76	959861	1 - 1945	15 - 1959	AW195880, AW028792, AI422839, AW296915, AW450528, AI978638, AI359463, AI688389, AI092026, AL138368, AI809106, AA405082,

					AI696811, AI241174, AI362203, AI751933, AI148259, AI760309, AI377870, AA764773, AI083661, AI452823, AI217412, AW291328, AI699316, AI858566, AI538545, AA694237, AA916467, AI424728, AW204251, AI356327, AI475515, AI378101, AI081264, AI762488, AW104976, AA515713, AI365463, H64877, AI400724, AI356328, H85225, T82265, AA843157, AA367751, AI243077, R36038, AA883597, AA325102, AI081265, AW086158, W01119, N58868, F07321, F07322, Z44523, N27294, N31581, F07356, AI370163, AA749270, H12737, T83552, AA878970, H84896, AI915401, N40032, AI872672, H03282, AA810842, W46869, W46820, AA443674, R56546, R06288, N87052, AA339608, AA252843, AA385629, and AB007956.
HETKR83	77	1225819	1 - 2219	15 - 2233	AW195777, AW269932, W29010, AI829559, AI571060, AI083491, AA905071, AW118125, AI376671, AI049799, AI393483, W22553, N90902, W27632, AI273588, AI890622, W22119, W27896, AI194027, N92239, AA040604, W23268, W38638, W37154, AA904910, W27944, R55894, W27681, C14616, AA337059, AW367713, AA897696, AA017680, C02576, H83294, C14877, AA298658, R55809, AA364393, W23093, W28670, W27851, AW086128, H83295, D81988, W27371, D60284, AA040705, AF122922, and AF122923.
HCUAZ04	78	1207329	1 - 714	15 - 728	AA723370, AI298971, AA854333, AI942475, AW328162, AW075555, AI376901, AI458456, AA775453, AI458455, AA782728, AA449945, AI051524, AI370872, AI188379, AI042548, AI193568, H72858, AA621746, AW071755, AI362906, AI884989, AI936998, AA847549, AA664042, AI936930, AA663982, N36925, AI497960, AI497929, AI244325, AI768357, AI287500, AA040876, AA181903, AA448965, H10076, AA970020, AA834370, AI698887, AI263335, AI016859, AI287835, AI192299, AI150936, AI219081, Z38369, AW135780, T99077, AI214680, AI350093, T91018, AI351313, AW150403, C01768, N36028, AA811294, AA449692, AA503553, N93835, N77563, AA766732, C04735, F07251, W03729, AA828413, AA907195, AA588280, AI539572, and AF151863.
HCE3J83	79	968823	1 - 539	15 - 553	AW069736, AA449593, AL079833,

					AA207229, AW444578, AW402682, AA471151, AF044588, and AC015841.
HAPOI67	80	971184	1 - 2190	15 - 2204	H70763, H70762, AW376414, AW403498, AI571894, AW450761, AF114491, AC004262, and AC005327.
HE8NIO5	81	1216548	1 - 2866	15 - 2880	AI468004, AI924049, AA243790, AI811485, AI828757, AA916944, AA620465, AL134851, AW023721, N70192, AA361686, AA894452, AA136774, AI187979, N98388, AW295746, T25746, and AF166350.
HHENW06	82	1040263	1 - 2535	15 - 2549	AI800218, AI346281, AI983710, AW026429, AI583539, AW264048, AI911743, AI766300, AI924093, AI264211, AI312053, AI201482, AI955668, AW058431, AW387854, AW196781, AI022218, AI565141, AI689249, AI276048, AI566956, AI920904, AW193090, AI623560, AA922838, AI306731, AW090493, AW299693, AI970021, AI983726, AI799761, AA526367, AW193893, AA453713, AI932812, AI800835, AI796911, R60430, C75200, H06926, H15208, W45378, AI280339, AA454508, AA194058, N26161, AI983692, T66357, AI798566, AA454904, F26986, AI653931, AA477573, T53415, AA159069, T56771, AI826240, D60131, AW168713, AW134730, AA496515, AI031629, AW167393, AA159059, AI701189, AI955982, F08019, AI244082, F06846, AW024803, AA720931, W40388, AW438920, AA496449, AA368933, AI382466, AW009728, AW176258, AW024804, AI910614, AW129533, AW070799, AW148513, H15148, AI434125, AW136838, AW073374, AA160862, AI269636, AW105266, AA454830, AA889374, AI683492, AI536855, AW268122, AW117746, AI886123, AI873644, AI432040, AW105431, AI445992, AI499986, AL036638, AW130930, AI445990, AI863191, AL045266, AA908294, AI697324, AL119791, AW302973, AI308035, AW268060, AW168031, AI866751, AI637748, AI280732, AI627880, AI866770, AI890907, AI886753, AW163823, AI886181, AI499285, AA569863, AI678357, AI537261, AI500523, AA704013, AI345416, AI345612, AW268302, AI538342, AI620089, AW072719, AW168485, AI933589, AI345131, AI270183, AW149925, AI863321, AI345415, AI874166, AI582932, AI921248, AI611738,

					AI476527, AI434741, AI619502, AW079572, AI632408, AI677796, AI802542, AA449768, AI288305, AI539028, AI288285, AW118518, AI570807, AI635067, AW026882, AI932794, AI923370, AI868931, AI620284, AI520809, AW003208, AI699865, AI886192, AI863382, AI433157, AW172723, AI702073, AI582483, AI783997, AI698391, AI783504, AL079963, AI913452, AI623941, AI500061, AI648663, AI689420, AW051088, AI633125, AI963846, AW051258, AI915291, AW152182, AI345477, AI866162, AI521560, AI889189, AI097410, AA872507, AI538764, AI866573, AI204298, AI801325, AI475377, AW089275, AI522052, AW238688, AI921281, AI499381, AI308032, AI349967, AI500662, AI473536, W74529, AI963346, AI344785, F27788, AL041772, AI888661, AI687689, AL121286, AI699011, AW071417, AI537515, AW083750, AI473554, AI860003, AI680453, AW129271, AL042628, AI174394, AW051226, AI784230, AI648473, AA494167, AL036403, AW163834, AL039086, AI358701, AI568138, AW162194, AI624293, AI636588, AW301754, AL037030, AI890223, AI857724, AI281782, AI567360, AW088899, AW148356, AI866741, AL038605, AL117551, L40459, AR012385, X72889, I89947, E03348, X96540, AL117432, A08913, AR059958, AR038854, A08916, AL133016, I48978, X93495, AR000496, U39656, U96683, U72620, A08910, A08909, AF008439, AL080060, AF061943, AF185576, AL137271, AL117585, A08912, I89931, AL117583, I49625, X63574, U67958, A65341, AL110280, S78214, AF026816, AF113019, AF100931, AJ012755, AL050149, AF090903, AL080159, L30117, AL137478, A77033, A77035, AF087943, Z82022, A93350, AF026124, AL137533, AL133560, I48979, AL117440, AF162270, Y07905, AL137292, AF113690, AF113689, L19437, E15569, AL080074, AJ238278, AL133557, U80742, AL050393, AF078844, AL049382, AF061795, AF151685, X65873, AF003737, AF067728, AL137550, I42402, X92070, AL110221, AF090900, AF081197, AF118094, AF153205, AL117460,
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					AL122098, Y09972, AF125948, AF090901, A03736, AL122121, AL137476, X82434, AL050024, AL049430, AF113699, E02349, AF111849, AF125949, AF113676, AF177401, AF032666, AR011880, I26207, AL049466, AF183393, AL137538, AF158248, AL080137, I33392, U35846, AF079765, AJ006417, AF106862, AL122123, AL049938, AL133645, AL080127, AL137463, AF104032, AF091084, AL133067, AF090934, AF113677, I03321, Y11587, Y14314, AL023657, AL137480, A58524, A58523, AL122110, S75997, AL137556, AL133665, AL050116, AL122118, U78525, E12747, AL133072, AL080124, AF119337, U00763, Y16645, AL049300, AL049452, AL049283, AL110196, AJ000937, AL133080, AL137560, U58996, AJ242859, AL117457, E08631, A45787, AL050108, AF090896, AL133565, AL137521, AF111112, E04233, I00734, AL110222, AF017437, AL117435, Z72491, A08908, AF111851, AL050172, AL117578, AF113013, E00617, E00717, E00778, AL050277, AL133606, AF057300, AF057299, AF079763, AF113694, AL137526, E06743, AL137557, E05822, AL137459, Z37987, AL049464, S79832, AF139986, AF022363, AF081195, X53587, U49908, S61953, AR038969, AL133104, AF097996, A90832, Y11254, AL133640, AF210052, AF113691, AF146568, AL122093, AL050092, AL050138, U42766, E02221, AB019565, AL122049, AF090943, AF118064, I09360, AL133093, X87582, AF118070, AL122050, X70685, AL049314, M30514, AL137648, AL133098, X84990, AF017152, E07108, A07647, and L31396.
HNSMB24	83	971537	1 - 671	15 - 685	AI978874, AI469095, AP001623, AP001623, AC015555, and AC015555.
HLMD077	84	974855	1 - 633	15 - 647	AI302099, D80253, D59859, C14389, D80366, D51423, D57483, D80188, D80227, D59889, D59467, D80166, D59619, D80210, D51799, D80240, D80269, D80391, D81030, D59787, D58283, D80212, D80022, D59275, D80248, C14331, D80219, D80024, D80195, D80196, D80164, D80043, D59502, D80251, AA305409, D59610, C14014, AA305578, D81026, D80133, D80378, D80522, AA514186, C15076, D59927, D80038, D50979, D51022, D50995, D80193, D80045, AW177440,

					AA514188, D80241, D51060, AW360811, D80268, AW178893, C14429, AW377671, AW375405, D80439, C75259, D80302, T03269, AW179328, D80247, D58253, AW366296, AW360844, AW360817, AW375406, AW378534, AW179332, AW377672, AW179023, AW178905, AW178906, AW177501, C05695, AW177511, AW378532, D80134, D59373, AW352171, AW377676, AW177505, AW352170, AW177731, D80132, AW178907, AW178762, AW179019, AW179024, D51079, D80157, D51103, D51250, AW360841, AW179012, AW179020, AW178775, D51759, AW367967, AW178909, AW177456, AW369651, AW352117, AW179329, AW178980, AW177733, AW378528, AW178908, AW178754, AW179018, AW352158, AW176467, AW179004, AW178914, AW378525, D80949, AW178983, AW352163, F13647, AW352174, T11417, T48593, C14227, D45260, D80168, AI910186, D59653, AW179009, C06015, AW177728, A62298, AR018138, AR008278, A84916, A62300, AB028859, AJ132110, AF058696, A82595, X67155, Y17188, D26022, Y12724, A25909, A67220, D89785, A78862, D34614, A94995, AB002449, AR060385, AR008443, D88547, I50126, I50132, I50128, I50133, X82626, I82448, AR066488, AR016514, AR060138, A45456, A26615, AR052274, AR054175, AR025207, I14842, Y09669, A43192, A43190, AR038669, AR066487, AR066490, A30438, I18367, AR008277, AR008281, D50010, Y17187, A63261, X64588, AR008408, AB012117, AR062872, A70867, AR016691, AR016690, U46128, X68127, D13509, A64136, A68321, AR060133, I79511, A85396, D88507, AR066482, A44171, A85477, I19525, A86792, X93549, U79457, AF123263, AR032065, X72378, and AR008382.
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TABLE 4

Code	Description	Tissue	Organ	Cell Line	Disease	Vector
AR022	a_Heart	a_Heart				
AR023	a_Liver	a_Liver				
AR024	a_mammary gland	a_mammary gland				
AR025	a_Prostate	a_Prostate				
AR026	a_small intestine	a_small intestine				
AR027	a_Stomach	a_Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1				
AR038	cell line transformed	cell line transformed				
AR039	colon	colon				
AR040	colon (9808co65R)	colon (9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR045	corn clone 5	corn clone 5				
AR046	corn clone 6	corn clone 6				
AR047	corn clone2	corn clone2				
AR048	corn clone3	corn clone3				
AR049	Corn Clone4	Corn Clone4				
AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs				
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs				
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.				
AR053	Donor II B-Cells 72hrs	Donor II B-Cells 72hrs				
AR054	Donor II Resting B Cells	Donor II Resting B Cells				
AR055	Heart	Heart				
AR056	Human Lung (clontech)	Human Lung (clontech)				
AR057	Human Mammary (clontech)	Human Mammary (clontech)				
AR058	Human Thymus (clontech)	Human Thymus (clontech)				
AR059	Jurkat (unstimulated)	Jurkat (unstimulated)				
AR060	Kidney	Kidney				
AR061	Liver	Liver				
AR062	Liver (Clontech)	Liver (Clontech)				
AR063	Lymphocytes chronic lymphocytic leukaemia	Lymphocytes chronic lymphocytic				

		leukaemia				
AR064	Lymphocytes diffuse large B cell lymphoma	Lymphocytes diffuse large B cell lymphoma				
AR065	Lymphocytes follicular lymphoma	Lymphocytes follicular lymphoma				
AR066	normal breast	normal breast				
AR067	Normal Ovarian (4004901)	Normal Ovarian (4004901)				
AR068	Normal Ovary 9508G045	Normal Ovary 9508G045				
AR069	Normal Ovary 9701G208	Normal Ovary 9701G208				
AR070	Normal Ovary 9806G005	Normal Ovary 9806G005				
AR071	Ovarian Cancer	Ovarian Cancer				
AR072	Ovarian Cancer (9702G001)	Ovarian Cancer (9702G001)				
AR073	Ovarian Cancer (9707G029)	Ovarian Cancer (9707G029)				
AR074	Ovarian Cancer (9804G011)	Ovarian Cancer (9804G011)				
AR075	Ovarian Cancer (9806G019)	Ovarian Cancer (9806G019)				
AR076	Ovarian Cancer (9807G017)	Ovarian Cancer (9807G017)				
AR077	Ovarian Cancer (9809G001)	Ovarian Cancer (9809G001)				
AR078	ovarian cancer 15799	ovarian cancer 15799				
AR079	Ovarian Cancer 17717AID	Ovarian Cancer 17717AID				
AR080	Ovarian Cancer 4004664B1	Ovarian Cancer 4004664B1				
AR081	Ovarian Cancer 4005315A1	Ovarian Cancer 4005315A1				
AR082	ovarian cancer 94127303	ovarian cancer 94127303				
AR083	Ovarian Cancer 96069304	Ovarian Cancer 96069304				
AR084	Ovarian Cancer 9707G029	Ovarian Cancer 9707G029				
AR085	Ovarian Cancer 9807G045	Ovarian Cancer 9807G045				
AR086	ovarian cancer 9809G001	ovarian cancer 9809G001				
AR087	Ovarian Cancer 9905C032RC	Ovarian Cancer 9905C032RC				
AR088	Ovarian cancer 9907 C00 3rd	Ovarian cancer 9907 C00 3rd				
AR089	Prostate	Prostate				
AR090	Prostate (clonotech)	Prostate (clonotech)				
AR091	prostate cancer	prostate cancer				
AR092	prostate cancer #15176	prostate cancer #15176				
AR093	prostate cancer #15509	prostate cancer #15509				
AR094	prostate cancer #15673	prostate cancer #15673				
AR095	Small Intestine (Clontech)	Small Intestine (Clontech)				
AR096	Spleen	Spleen				

AR097	Thymus T cells activated	Thymus T cells activated				
AR098	Thymus T cells resting	Thymus T cells resting				
AR099	Tonsil	Tonsil				
AR100	Tonsil germinal center centroblast	Tonsil germinal center centroblast				
AR101	Tonsil germinal center B cell	Tonsil germinal center B cell				
AR102	Tonsil lymph node	Tonsil lymph node				
AR103	Tonsil memory B cell	Tonsil memory B cell				
AR104	Whole Brain	Whole Brain				
AR105	Xenograft ES-2	Xenograft ES-2				
AR106	Xenograft SW626	Xenograft SW626				
H0004	Human Adult Spleen	Human Adult Spleen	Spleen			Uni-ZAP XR
H0009	Human Fetal Brain					Uni-ZAP XR
H0012	Human Fetal Kidney	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0013	Human 8 Week Whole Embryo	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR
H0014	Human Gall Bladder	Human Gall Bladder	Gall Bladder			Uni-ZAP XR
H0017	Human Greater Omentum	Human Greater Omentum	peritoneum			Uni-ZAP XR
H0024	Human Fetal Lung III	Human Fetal Lung	Lung			Uni-ZAP XR
H0026	Namalwa Cells	Namalwa B-Cell Line, EBV immortalized				Lambda ZAP II
H0028	Human Old Ovary	Human Old Ovary	Ovary			pBluescript
H0030	Human Placenta					Uni-ZAP XR
H0031	Human Placenta	Human Placenta	Placenta			Uni-ZAP XR
H0032	Human Prostate	Human Prostate	Prostate			Uni-ZAP XR
H0036	Human Adult Small Intestine	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0038	Human Testes	Human Testes	Testis			Uni-ZAP XR
H0039	Human Pancreas Tumor	Human Pancreas Tumor	Pancreas	disease		Uni-ZAP XR
H0040	Human Testes Tumor	Human Testes Tumor	Testis	disease		Uni-ZAP XR
H0041	Human Fetal Bone	Human Fetal Bone	Bone			Uni-ZAP XR
H0042	Human Adult Pulmonary	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0046	Human Endometrial Tumor	Human Endometrial Tumor	Uterus	disease		Uni-ZAP XR
H0050	Human Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0051	Human Hippocampus	Human Hippocampus	Brain			Uni-ZAP XR
H0052	Human Cerebellum	Human Cerebellum	Brain			Uni-ZAP XR
H0056	Human Umbilical Vein, Endo. remake	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0057	Human Fetal Spleen					Uni-ZAP XR
H0059	Human Uterine Cancer	Human Uterine Cancer	Uterus	disease		Lambda ZAP II
H0063	Human Thymus	Human Thymus	Thymus			Uni-ZAP XR
H0068	Human Skin Tumor	Human Skin Tumor	Skin	disease		Uni-ZAP XR
H0069	Human Activated T-Cells	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0071	Human Infant Adrenal Gland	Human Infant Adrenal Gland	Adrenal gland			Uni-ZAP XR
H0075	Human Activated T-Cells (II)	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0081	Human Fetal Epithelium	Human Fetal Skin	Skin			Uni-ZAP XR

	(Skin)					
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Jurkat Cells				Uni-ZAP XR
H0086	Human epithelioid sarcoma	Epithelioid Sarcoma, muscle	Sk Muscle		disease	Uni-ZAP XR
H0087	Human Thymus	Human Thymus				pBluescript
H0090	Human T-Cell Lymphoma	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0100	Human Whole Six Week Old Embryo	Human Whole Six Week Old Embryo	Embryo			Uni-ZAP XR
H0105	Human Fetal Heart, subtracted	Human Fetal Heart	Heart			pBluescript
H0122	Human Adult Skeletal Muscle	Human Skeletal Muscle	Sk Muscle			Uni-ZAP XR
H0123	Human Fetal Dura Mater	Human Fetal Dura Mater	Brain			Uni-ZAP XR
H0124	Human Rhabdomyosarcoma	Human Rhabdomyosarcoma	Sk Muscle		disease	Uni-ZAP XR
H0125	Cem cells cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0132	LNCAP + 30nM R1881	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
H0135	Human Synovial Sarcoma	Human Synovial Sarcoma	Synovium			Uni-ZAP XR
H0136	Supt Cells, cyclohexamide treated	Cyclohexamide Treated Cem, Jurkat, Raji, and Supt	Blood	Cell Line		Uni-ZAP XR
H0144	Nine Week Old Early Stage Human	9 Wk Old Early Stage Human	Embryo			Uni-ZAP XR
H0150	Human Epididymus	Epididymis	Testis			Uni-ZAP XR
H0156	Human Adrenal Gland Tumor	Human Adrenal Gland Tumor	Adrenal Gland		disease	Uni-ZAP XR
H0163	Human Synovium	Human Synovium	Synovium			Uni-ZAP XR
H0166	Human Prostate Cancer, Stage B2 fraction	Human Prostate Cancer, stage B2	Prostate		disease	Uni-ZAP XR
H0169	Human Prostate Cancer, Stage C fraction	Human Prostate Cancer, stage C	Prostate		disease	Uni-ZAP XR
H0170	12 Week Old Early Stage Human	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0171	12 Week Old Early Stage Human, II	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0181	Human Primary Breast Cancer	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0188	Human Normal Breast	Human Normal Breast	Breast			Uni-ZAP XR
H0194	Human Cerebellum, subtracted	Human Cerebellum	Brain			pBluescript
H0208	Early Stage Human Lung, subtracted	Human Fetal Lung	Lung			pBluescript
H0212	Human Prostate, subtracted	Human Prostate	Prostate			pBluescript
H0213	Human Pituitary, subtracted	Human Pituitary				Uni-ZAP XR
H0218	Activated T-Cells, 0hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0222	Activated T-Cells, 8 hrs, subtracted	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0231	Human Colon, subtraction	Human Colon				pBluescript
H0239	Human Kidney Tumor	Human Kidney Tumor	Kidney		disease	Uni-ZAP XR
H0244	Human 8 Week Whole Embryo, subtracted	Human 8 Week Old Embryo	Embryo			Uni-ZAP XR

H0251	Human Chondrosarcoma	Human Chondrosarcoma	Cartilage		disease	Uni-ZAP XR
H0252	Human Osteosarcoma	Human Osteosarcoma	Bone		disease	Uni-ZAP XR
H0255	breast lymph node CDNA library	Breast Lymph Node	Lymph Node			Lambda ZAP II
H0261	H. cerebellum, Enzyme subtracted	Human Cerebellum	Brain			Uni-ZAP XR
H0263	human colon cancer	Human Colon Cancer	Colon		disease	Lambda ZAP II
H0264	human tonsils	Human Tonsil	Tonsil			Uni-ZAP XR
H0265	Activated T-Cell (12hs)/Thiouridine labelledEco	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0266	Human Microvascular Endothelial Cells, fract. A	HMEC	Vein	Cell Line		Lambda ZAP II
H0270	HPAS (human pancreas, subtracted)	Human Pancreas	Pancreas			Uni-ZAP XR
H0271	Human Neutrophil, Activated	Human Neutrophil - Activated	Blood	Cell Line		Uni-ZAP XR
H0272	HUMAN TONSILS, FRACTION 2	Human Tonsil	Tonsil			Uni-ZAP XR
H0284	Human OB MG63 control fraction I.	Human Osteoblastoma MG63 cell line	Bone	Cell Line		Uni-ZAP XR
H0288	Human OB HOS control fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0292	Human OB HOS treated (10 nM E2) fraction I	Human Osteoblastoma HOS cell line	Bone	Cell Line		Uni-ZAP XR
H0295	Amniotic Cells - Primary Culture	Amniotic Cells - Primary Culture	Placenta	Cell Line		Uni-ZAP XR
H0305	CD34 positive cells (Cord Blood)	CD34 Positive Cells	Cord Blood			ZAP Express
H0306	CD34 depleted Buffy Coat (Cord Blood)	CD34 Depleted Buffy Coat (Cord Blood)	Cord Blood			ZAP Express
H0309	Human Chronic Synovitis	Synovium, Chronic Synovitis/ Osteoarthritis	Synovium		disease	Uni-ZAP XR
H0310	human caudate nucleus	Brain	Brain			Uni-ZAP XR
H0316	HUMAN STOMACH	Human Stomach	Stomach			Uni-ZAP XR
H0318	HUMAN B CELL LYMPHOMA	Human B Cell Lymphoma	Lymph Node		disease	Uni-ZAP XR
H0328	human ovarian cancer	Ovarian Cancer	Ovary		disease	Uni-ZAP XR
H0329	Dermatofibrosarcoma Protuberance	Dermatofibrosarcoma Protuberans	Skin		disease	Uni-ZAP XR
H0331	Hepatocellular Tumor	Hepatocellular Tumor	Liver		disease	Lambda ZAP II
H0333	Hemangiopericytoma	Hemangiopericytoma	Blood vessel		disease	Lambda ZAP II
H0341	Bone Marrow Cell Line (RS4;11)	Bone Marrow Cell Line RS4;11	Bone Marrow	Cell Line		Uni-ZAP XR
H0352	wilm's tumor	Wilm's Tumor			disease	Uni-ZAP XR
H0355	Human Liver	Human Liver, normal Adult				pCMVSPORT 1
H0369	H. Atrophic Endometrium	Atrophic Endometrium and myometrium				Uni-ZAP XR
H0370	H. Lymph node breast Cancer	Lymph node with Met. Breast Cancer			disease	Uni-ZAP XR

H0373	Human Heart	Human Adult Heart	Heart			pCMVSPORT 1
H0375	Human Lung	Human Lung				pCMVSPORT 1
H0380	Human Tongue, frac 2	Human Tongue				pSPORT1
H0381	Bone Cancer	Bone Cancer			disease	Uni-ZAP XR
H0386	Leukocyte and Lung; 4 screens	Human Leukocytes	Blood	Cell Line		pCMVSPORT 1
H0392	H. Meningioma, M1	Human Meningioma	brain			pSPORT1
H0393	Fetal Liver, subtraction II	Human Fetal Liver	Liver			pBluescript
H0411	H Female Bladder, Adult	Human Female Adult Bladder	Bladder			pSPORT1
H0412	Human umbilical vein endothelial cells, IL-4 induced	HUVE Cells	Umbilical vein	Cell Line		pSPORT1
H0413	Human Umbilical Vein Endothelial Cells, uninduced	HUVE Cells	Umbilical vein	Cell Line		pSPORT1
H0414	Ovarian Tumor I, OV5232	Ovarian Tumor, OV5232	Ovary		disease	pSPORT1
H0415	H. Ovarian Tumor, II, OV5232	Ovarian Tumor, OV5232	Ovary		disease	pCMVSPORT 2.0
H0418	Human Pituitary, subtracted VII	Human Pituitary				pBluescript
H0422	T-Cell PHA 16 hrs	T-Cells	Blood	Cell Line		pSPORT1
H0423	T-Cell PHA 24 hrs	T-Cells	Blood	Cell Line		pSPORT1
H0424	Human Pituitary, subt IX	Human Pituitary				pBluescript
H0427	Human Adipose	Human Adipose, left lipoma				pSPORT1
H0428	Human Ovary	Human Ovary Tumor	Ovary			pSPORT1
H0429	K562 + PMA (36 hrs), re-excision	K562 Cell line	cell line	Cell Line		ZAP Express
H0431	H. Kidney Medulla, re-excision	Kidney medulla	Kidney			pBluescript
H0434	Human Brain, striatum, re-excision	Human Brain, Striatum				pBluescript
H0435	Ovarian Tumor 10-3-95	Ovarian Tumor, OV350721	Ovary			pCMVSPORT 2.0
H0438	H. Whole Brain #2, re-excision	Human Whole Brain #2				ZAP Express
H0439	Human Eosinophils	Eosinophils				pBluescript
H0441	H. Kidney Cortex, subtracted	Kidney cortex	Kidney			pBluescript
H0444	Spleen metastatic melanoma	Spleen, Metastatic malignant melanoma	Spleen		disease	pSPORT1
H0445	Spleen, Chronic lymphocytic leukemia	Human Spleen, CLL	Spleen		disease	pSPORT1
H0455	H. Striatum Depression, subt	Human Brain, Striatum Depression	Brain			pBluescript
H0457	Human Eosinophils	Human Eosinophils				pSPORT1
H0477	Human Tonsil, Lib 3	Human Tonsil	Tonsil			pSPORT1
H0478	Salivary Gland, Lib 2	Human Salivary Gland	Salivary gland			pSPORT1
H0483	Breast Cancer cell line, MDA 36	Breast Cancer Cell line, MDA 36				pSPORT1
H0486	Hodgkin's Lymphoma II	Hodgkin's Lymphoma II			disease	pCMVSPORT 2.0
H0494	Keratinocyte	Keratinocyte				pCMVSPORT 2.0
H0497	HEL cell line	HEL cell line		HEL 92.1.7		pSPORT1
H0506	Ulcerative Colitis	Colon	Colon			pSPORT1

H0509	Liver, Hepatoma	Human Liver, Hepatoma, patient 8	Liver		disease	pCMVSPORT 3.0
H0510	Human Liver, normal	Human Liver, normal, Patient # 8	Liver			pCMVSPORT 3.0
H0518	pBMC stimulated w/ poly I/C	pBMC stimulated with poly I/C				pCMVSPORT 3.0
H0519	NTERA2, control	NTERA2, Teratocarcinoma cell line				pCMVSPORT 3.0
H0520	NTERA2 + retinoic acid, 14 days	NTERA2, Teratocarcinoma cell line				pSPORT1
H0521	Primary Dendritic Cells, lib 1	Primary Dendritic cells				pCMVSPORT 3.0
H0522	Primary Dendritic cells, frac 2	Primary Dendritic cells				pCMVSPORT 3.0
H0529	Myeloid Progenitor Cell Line	TF-1 Cell Line; Myeloid progenitor cell line				pCMVSPORT 3.0
H0535	Human ovary tumor cell OV350721	Ovarian Tumor, OV350721	Ovary		disease	pSPORT1
H0538	Merkel Cells	Merkel cells	Lymph node			pSPORT1
H0539	Pancreas Islet Cell Tumor	Pancreas Islet Cell Tumour	Pancreas		disease	pSPORT1
H0542	T Cell helper I	Helper T cell				pCMVSPORT 3.0
H0543	T cell helper II	Helper T cell				pCMVSPORT 3.0
H0544	Human endometrial stromal cells	Human endometrial stromal cells				pCMVSPORT 3.0
H0545	Human endometrial stromal cells-treated with progesterone	Human endometrial stromal cells-treated with proge				pCMVSPORT 3.0
H0546	Human endometrial stromal cells-treated with estradiol	Human endometrial stromal cells-treated with estra				pCMVSPORT 3.0
H0547	NTERA2 teratocarcinoma cell line+retinoic acid (14 days)	NTERA2, Teratocarcinoma cell line				pSPORT1
H0549	H. Epididymus, caput & corpus	Human Epididymus, caput and corpus				Uni-ZAP XR
H0550	H. Epididymus, cauda	Human Epididymus, cauda				Uni-ZAP XR
H0551	Human Thymus Stromal Cells	Human Thymus Stromal Cells				pCMVSPORT 3.0
H0553	Human Placenta	Human Placenta				pCMVSPORT 3.0
H0555	Rejected Kidney, lib 4	Human Rejected Kidney	Kidney		disease	pCMVSPORT 3.0
H0556	Activated T-cell(12h)/Thiouridine-re-excision	T-Cells	Blood	Cell Line		Uni-ZAP XR
H0559	HL-60, PMA 4H, re-excision	HL-60 Cells, PMA stimulated 4H	Blood	Cell Line		Uni-ZAP XR
H0560	KMH2	KMH2				pCMVSPORT 3.0
H0561	L428	L428				pCMVSPORT 3.0
H0562	Human Fetal Brain, normalized c5-11-26	Human Fetal Brain				pCMVSPORT 2.0
H0569	Human Fetal Brain,	Human Fetal Brain				pCMVSPORT

	normalized CO					2.0
H0574	Hepatocellular Tumor; re-excision	Hepatocellular Tumor	Liver		disease	Lambda ZAP II
H0575	Human Adult Pulmonary; re-excision	Human Adult Pulmonary	Lung			Uni-ZAP XR
H0576	Resting T-Cell; re-excision	T-Cells	Blood	Cell Line		Lambda ZAP II
H0578	Human Fetal Thymus	Fetal Thymus	Thymus			pSport1
H0580	Dendritic cells, pooled	Pooled dendritic cells				pCMVSPORT 3.0
H0581	Human Bone Marrow, treated	Human Bone Marrow	Bone Marrow			pCMVSPORT 3.0
H0586	Healing groin wound, 6.5 hours post incision	healing groin wound, 6.5 hours post incision - 2/	groin		disease	pCMVSPORT 3.0
H0587	Healing groin wound; 7.5 hours post incision	Groin-2/19/97	groin		disease	pCMVSPORT 3.0
H0590	Human adult small intestine; re-excision	Human Adult Small Intestine	Small Int.			Uni-ZAP XR
H0591	Human T-cell lymphoma; re-excision	T-Cell Lymphoma	T-Cell		disease	Uni-ZAP XR
H0592	Healing groin wound - zero hr post-incision (control)	HGS wound healing project; abdomen			disease	pCMVSPORT 3.0
H0593	Olfactory epithelium; nasalcavity	Olfactory epithelium from roof of left nasal cavity				pCMVSPORT 3.0
H0596	Human Colon Cancer; re-excision	Human Colon Cancer	Colon			Lambda ZAP II
H0597	Human Colon; re-excision	Human Colon				Lambda ZAP II
H0598	Human Stomach; re-excision	Human Stomach	Stomach			Uni-ZAP XR
H0599	Human Adult Heart; re-excision	Human Adult Heart	Heart			Uni-ZAP XR
H0604	Human Pituitary, re-excision	Human Pituitary				pBluescript
H0610	H. Leukocytes, normalized cot 5A	H. Leukocytes				pCMVSPORT 1
H0615	Human Ovarian Cancer Reexcision	Ovarian Cancer	Ovary		disease	Uni-ZAP XR
H0616	Human Testes, Reexcision	Human Testes	Testis			Uni-ZAP XR
H0617	Human Primary Breast Cancer Reexcision	Human Primary Breast Cancer	Breast		disease	Uni-ZAP XR
H0618	Human Adult Testes, Large Inserts, Reexcision	Human Adult Testis	Testis			Uni-ZAP XR
H0619	Fetal Heart	Human Fetal Heart	Heart			Uni-ZAP XR
H0620	Human Fetal Kidney; Reexcision	Human Fetal Kidney	Kidney			Uni-ZAP XR
H0622	Human Pancreas Tumor; Reexcision	Human Pancreas Tumor	Pancreas		disease	Uni-ZAP XR
H0623	Human Umbilical Vein; Reexcision	Human Umbilical Vein Endothelial Cells	Umbilical vein			Uni-ZAP XR
H0624	12 Week Early Stage Human II; Reexcision	Twelve Week Old Early Stage Human	Embryo			Uni-ZAP XR
H0625	Ku 812F Basophils Line	Ku 812F Basophils				pSport1
H0626	Saos2 Cells; Untreated	Saos2 Cell Line; Untreated				pSport1
H0628	Human Pre-Differentiated Adipocytes	Human Pre-Differentiated Adipocytes				Uni-ZAP XR

H0631	Saos2, Dexamethosome Treated	Saos2 Cell Line; Dexamethosome Treated				pSport1
H0632	Hepatocellular Tumor; re-excision	Hepatocellular Tumor	Liver			Lambda ZAP II
H0633	Lung Carcinoma A549, TNFalpha activated	TNFalpha activated A549--Lung Carcinoma			disease	pSport1
H0634	Human Testes Tumor, re-excision	Human Testes Tumor	Testis		disease	Uni-ZAP XR
H0635	Human Activated T-Cells, re-excision	Activated T-Cells	Blood	Cell Line		Uni-ZAP XR
H0636	Chondrocytes	Chondrocytes				pSport1
H0638	CD40 activated monocyte dendritic cells	CD40 activated monocyte dendritic cells				pSport1
H0641	LPS activated derived dendritic cells	LPS activated monocyte derived dendritic cells				pSport1
H0643	Hep G2 Cells, PCR library	Hep G2 Cells				Other
H0644	Human Placenta (re-excision)	Human Placenta	Placenta			Uni-ZAP XR
H0645	Fetal Heart, re-excision	Human Fetal Heart	Heart			Uni-ZAP XR
H0646	Lung, Cancer (4005313 A3): Invasive Poorly Differentiated Lung Adenocarcinoma,	Metastatic squamous cell lung carcinoma, poorly di				pSport1
H0647	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	Invasive poorly differentiated lung adenocarcinoma			disease	pSport1
H0648	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot	Papillary Cstic neoplasm of low malignant potentia			disease	pSport1
H0649	Lung, Normal: (4005313 B1)	Normal Lung				pSport1
H0650	B-Cells	B-Cells				pCMVSPORT 3.0
H0651	Ovary, Normal: (9805C040R)	Normal Ovary				pSport1
H0652	Lung, Normal: (4005313 B1)	Normal Lung				pSport1
H0656	B-cells (unstimulated)	B-cells (unstimulated)				pSport1
H0657	B-cells (stimulated)	B-cells (stimulated)				pSport1
H0658	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	9809C332- Poorly differentiate	Ovary & Fallopian Tubes		disease	pSport1
H0659	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	Grade II Papillary Carcinoma, Ovary	Ovary		disease	pSport1
H0660	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	Poorly differentiated carcinoma, ovary			disease	pSport1
H0661	Breast, Cancer: (4004943 A5)	Breast cancer			disease	pSport1
H0662	Breast, Normal: (4005522B2)	Normal Breast - #4005522(B2)	Breast			pSport1
H0663	Breast, Cancer: (4005522 A2)	Breast Cancer - #4005522(A2)	Breast		disease	pSport1
H0664	Breast, Cancer:	Breast Cancer	Breast		disease	pSport1

	(9806C012R)					
H0665	Stromal cells 3.88	Stromal cells 3.88				pSport1
H0667	Stromal cells(HBM3.18)	Stromal cell(HBM 3.18)				pSport1
H0669	Breast, Cancer: (4005385 A2)	Breast Cancer (4005385A2)	Breast			pSport1
H0670	Ovary, Cancer(4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	Ovarian Cancer - 4004650A3				pSport1
H0672	Ovary, Cancer: (4004576 A8)	Ovarian Cancer(4004576A8)	Ovary			pSport1
H0673	Human Prostate Cancer, Stage B2; re-excision	Human Prostate Cancer, stage B2	Prostate			Uni-ZAP XR
H0674	Human Prostate Cancer, Stage C; re-excision	Human Prostate Cancer, stage C	Prostate			Uni-ZAP XR
H0675	Colon, Cancer: (9808C064R)	Colon Cancer 9808C064R				pCMVSPORT 3.0
H0677	TNFR degenerate oligo	B-Cells				PCR11
H0682	Serous Papillary Adenocarcinoma	serous papillary adenocarcinoma (9606G304SPA3B)				pCMVSPORT 3.0
H0683	Ovarian Serous Papillary Adenocarcinoma	Serous papillary adenocarcinoma, stage 3C (9804G01)				pCMVSPORT 3.0
H0684	Serous Papillary Adenocarcinoma	Ovarian Cancer- 9810G606	Ovaries			pCMVSPORT 3.0
H0686	Adenocarcinoma of Ovary, Human Cell Line	Adenocarcinoma of Ovary, Human Cell Line, # SW-626				pCMVSPORT 3.0
H0687	Human normal ovary(#9610G215)	Human normal ovary(#9610G215)	Ovary			pCMVSPORT 3.0
H0689	Ovarian Cancer	Ovarian Cancer, #9806G019				pCMVSPORT 3.0
H0690	Ovarian Cancer, # 9702G001	Ovarian Cancer, #9702G001				pCMVSPORT 3.0
H0694	Prostate gland adenocarcinoma	Prostate gland, adenocarcinoma, mod/diff, gleason	prostate gland			pCMVSPORT 3.0
H0695	mononucleocytes from patient	mononucleocytes from patient at Shady Grove Hospit				pCMVSPORT 3.0
S0002	Monocyte activated	Monocyte-activated	blood	Cell Line		Uni-ZAP XR
S0003	Human Osteoclastoma	Osteoclastoma	bone		disease	Uni-ZAP XR
S0007	Early Stage Human Brain	Human Fetal Brain				Uni-ZAP XR
S0010	Human Amygdala	Amygdala				Uni-ZAP XR
S0024	Human Kidney Medulla - unamplified	Human Kidney Medulla				
S0026	Stromal cell TF274	stromal cell	Bone marrow	Cell Line		Uni-ZAP XR
S0027	Smooth muscle, serum treated	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0028	Smooth muscle, control	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0031	Spinal cord	Spinal cord	spinal cord			Uni-ZAP XR
S0036	Human Substantia Nigra	Human Substantia Nigra				Uni-ZAP XR
S0037	Smooth muscle, IL1b induced	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0038	Human Whole Brain #2 - Oligo dT > 1.5Kb	Human Whole Brain #2				ZAP Express
S0040	Adipocytes	Human Adipocytes from Osteoclastoma				Uni-ZAP XR

S0042	Testes	Human Testes				ZAP Express
S0044	Prostate BPH	prostate BPH	Prostate		disease	Uni-ZAP XR
S0045	Endothelial cells-control	Endothelial cell	endothelial cell-lung	Cell Line		Uni-ZAP XR
S0046	Endothelial-induced	Endothelial cell	endothelial cell-lung	Cell Line		Uni-ZAP XR
S0049	Human Brain, Striatum	Human Brain, Striatum				Uni-ZAP XR
S0050	Human Frontal Cortex, Schizophrenia	Human Frontal Cortex, Schizophrenia			disease	Uni-ZAP XR
S0051	Human Hypothalamus, Schizophrenia	Human Hypothalamus, Schizophrenia			disease	Uni-ZAP XR
S0052	neutrophils control	human neutrophils	blood	Cell Line		Uni-ZAP XR
S0053	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0110	Brain Amygdala Depression		Brain		disease	Uni-ZAP XR
S0112	Hypothalamus		Brain			Uni-ZAP XR
S0114	Anergic T-cell	Anergic T-cell		Cell Line		Uni-ZAP XR
S0116	Bone marrow	Bone marrow	Bone marrow			Uni-ZAP XR
S0126	Osteoblasts	Osteoblasts	Knee	Cell Line		Uni-ZAP XR
S0132	Epithelial-TNF α and INF induced	Airway Epithelial				Uni-ZAP XR
S0134	Apoptotic T-cell	apoptotic cells		Cell Line		Uni-ZAP XR
S0142	Macrophage-oxLDL	macrophage-oxidized LDL treated	blood	Cell Line		Uni-ZAP XR
S0144	Macrophage (GM-CSF treated)	Macrophage (GM-CSF treated)				Uni-ZAP XR
S0146	prostate-edited	prostate BPH	Prostate			Uni-ZAP XR
S0150	LNCAP prostate cell line	LNCAP Cell Line	Prostate	Cell Line		Uni-ZAP XR
S0152	PC3 Prostate cell line	PC3 prostate cell line				Uni-ZAP XR
S0192	Synovial Fibroblasts (control)	Synovial Fibroblasts				pSport1
S0194	Synovial hypoxia	Synovial Fibroblasts				pSport1
S0196	Synovial IL-1/TNF stimulated	Synovial Fibroblasts				pSport1
S0206	Smooth Muscle- HASTE normalized	Smooth muscle	Pulmonary artery	Cell Line		pBluescript
S0210	Mesangial cell, frac 2	Mesangial cell				pSport1
S0212	Bone Marrow Stromal Cell, untreated	Bone Marrow Stromal Cell, untreated				pSport1
S0214	Human Osteoclastoma, re-excision	Osteoclastoma	bone		disease	Uni-ZAP XR
S0216	Neutrophils IL-1 and LPS induced	human neutrophil induced	blood	Cell Line		Uni-ZAP XR
S0222	H. Frontal cortex, epileptic; re-excision	H. Brain, Frontal Cortex, Epileptic	Brain		disease	Uni-ZAP XR
S0242	Synovial Fibroblasts (IL1/TNF), subt	Synovial Fibroblasts				pSport1
S0250	Human Osteoblasts II	Human Osteoblasts	Femur		disease	pCMVSPORT 2.0
S0260	Spinal Cord, re-excision	Spinal cord	spinal cord			Uni-ZAP XR
S0276	Synovial hypoxia-RSF subtracted	Synovial fibroblasts (rheumatoid)	Synovial tissue			pSport1
S0278	H Macrophage (GM-CSF treated), re-excision	Macrophage (GM-CSF treated)				Uni-ZAP XR

S0280	Human Adipose Tissue, re-excision	Human Adipose Tissue				Uni-ZAP XR
S0282	Brain Frontal Cortex, re-excision	Brain frontal cortex	Brain			Lambda ZAP II
S0294	Larynx tumor	Larynx tumor	Larynx, vocal cord		disease	pSport1
S0300	Frontal lobe, dementia; re-excision	Frontal Lobe, dementia/Alzheimer's	Brain			Uni-ZAP XR
S0328	Palate carcinoma	Palate carcinoma	Uvula		disease	pSport1
S0330	Palate normal	Palate normal	Uvula			pSport1
S0332	Pharynx carcinoma	Pharynx carcinoma	Hypopharynx			pSport1
S0338	Human Osteoarthritic Cartilage Fraction III	Human osteoarthritic cartilage			disease	pSport1
S0340	Human Osteoarthritic Cartilage Fraction IV	Human osteoarthritic cartilage			disease	pSport1
S0346	Human Amygdala; re-excision	Amygdala				Uni-ZAP XR
S0354	Colon Normal II	Colon Normal	Colon			pSport1
S0356	Colon Carcinoma	Colon Carcinoma	Colon		disease	pSport1
S0358	Colon Normal III	Colon Normal	Colon			pSport1
S0360	Colon Tumor II	Colon Tumor	Colon		disease	pSport1
S0362	Human Gastrocnemius	Gastrocnemius muscle				pSport1
S0364	Human Quadriceps	Quadriceps muscle				pSport1
S0366	Human Soleus	Soleus Muscle				pSport1
S0374	Normal colon	Normal colon				pSport1
S0376	Colon Tumor	Colon Tumor			disease	pSport1
S0378	Pancreas normal PCA4 No	Pancreas Normal PCA4 No				pSport1
S0380	Pancreas Tumor PCA4 Tu	Pancreas Tumor PCA4 Tu			disease	pSport1
S0386	Human Whole Brain, re-excision	Whole brain	Brain			ZAP Express
S0388	Human Hypothalamus, schizophrenia, re-excision	Human Hypothalamus, Schizophrenia			disease	Uni-ZAP XR
S0390	Smooth muscle, control; re-excision	Smooth muscle	Pulmonary artery	Cell Line		Uni-ZAP XR
S0400	Brain; normal	Brain; normal				pSport1
S0408	Colon, normal	Colon, normal				pSport1
S0412	Temporal cortex-Alzheimer; subtracted	Temporal cortex, alzheimer			disease	Other
S0418	CHME Cell Line; treated 5 hrs	CHME Cell Line; treated				pCMVSPORT 3.0
S0420	CHME Cell Line, untreated	CHME Cell line, untreated				pSport1
S0422	Mo7e Cell Line GM-CSF treated (1ng/ml)	Mo7e Cell Line GM-CSF treated (1ng/ml)				pCMVSPORT 3.0
S0424	TF-1 Cell Line GM-CSF Treated	TF-1 Cell Line GM-CSF Treated				pSport1
S0430	Aryepiglottis Normal	Aryepiglottis Normal				pSport1
S0434	Stomach Normal	Stomach Normal			disease	pSport1
S0436	Stomach Tumour	Stomach Tumour			disease	pSport1
S0450	Larynx Tumour	Larynx Tumour				pSport1
S0468	Ea.hy.926 cell line	Ea.hy.926 cell line				pSport1
S0472	Lung Mesothelium	PYBT				pSport1
S3012	Smooth Muscle Serum	Smooth muscle	Pulmonary	Cell Line		pBluescript

	Treated, Norm		artery			
S3014	Smooth muscle, serum induced, re-exc	Smooth muscle	Pulmonary artery	Cell Line		pBluescript
S6016	H. Frontal Cortex, Epileptic	H. Brain, Frontal Cortex, Epileptic	Brain		disease	Uni-ZAP XR
S6022	H. Adipose Tissue	Human Adipose Tissue				Uni-ZAP XR
S6024	Alzheimers, spongy change	Alzheimer's/Spongy change	Brain		disease	Uni-ZAP XR
S6026	Frontal Lobe, Dementia	Frontal Lobe dementia/Alzheimer's	Brain			Uni-ZAP XR
S6028	Human Manic Depression Tissue	Human Manic depression tissue	Brain		disease	Uni-ZAP XR
T0002	Activated T-cells	Activated T-Cell, PBL fraction	Blood	Cell Line		pBluescript SK-
T0003	Human Fetal Lung	Human Fetal Lung				pBluescript SK-
T0006	Human Pineal Gland	Human Pineal Gland				pBluescript SK-
T0010	Human Infant Brain	Human Infant Brain				Other
T0041	Jurkat T-cell-G1 phase	Jurkat T-cell				pBluescript SK-
T0042	Jurkat T-Cell, S phase	Jurkat T-Cell Line				pBluescript SK-
T0047	T lymphocytes >70	T lymphocytes > 70				pBluescript SK-
T0049	Aorta endothelial cells + TNF-a	Aorta endothelial cells				pBluescript SK-
T0060	Human White Adipose	Human White Fat				pBluescript SK-
T0067	Human Thyroid	Human Thyroid				pBluescript SK-
T0069	Human Uterus, normal	Human Uterus, normal				pBluescript SK-
T0082	Human Adult Retina	Human Adult Retina				pBluescript SK-
T0110	Human colon carcinoma (HCC) cell line, remake					pBluescript SK-
T0115	Human Colon Carcinoma (HCC) cell line					pBluescript SK-
L0005	Clontech human aorta polyA+ mRNA (#6572)					
L0015	Human					
L0021	Human adult (K.Okubo)					
L0055	Human promyelocyte					
L0142	Human placenta cDNA (TFujiwara)	placenta				
L0143	Human placenta polyA+ (TFujiwara)	placenta				
L0157	Human fetal brain (TFujiwara)		brain			
L0163	Human heart cDNA (YNakamura)		heart			
L0352	Normalized infant brain, Bento Soares					BA, M13-derived
L0362	Stratagene ovarian cancer (#937219)					Bluescript SK-
L0364	NCL CGAP_GCS	germ cell tumor				Bluescript SK-
L0366	Stratagene schizo brain S11	schizophrenic brain S-11 frontal lobe				Bluescript SK-

L0368	NCI_CGAP_SS1	synovial sarcoma				Bluescript SK-
L0369	NCI_CGAP_AA1	adrenal adenoma	adrenal gland			Bluescript SK-
L0371	NCI_CGAP_Br3	breast tumor	breast			Bluescript SK-
L0372	NCI_CGAP_Co12	colon tumor	colon			Bluescript SK-
L0375	NCI_CGAP_Kid6	kidney tumor	kidney			Bluescript SK-
L0376	NCI_CGAP_Lar1	larynx	larynx			Bluescript SK-
L0378	NCI_CGAP_Lu1	lung tumor	lung			Bluescript SK-
L0381	NCI_CGAP_HN4	squamous cell carcinoma	pharynx			Bluescript SK-
L0383	NCI_CGAP_Pr24	invasive tumor (cell line)	prostate			Bluescript SK-
L0384	NCI_CGAP_Pr23	prostate tumor	prostate			Bluescript SK-
L0387	NCI_CGAP_GCB0	germinal center B-cells	tonsil			Bluescript SK-
L0389	NCI_CGAP_HN5	normal gingiva (cell line from primary keratinocyt				Bluescript SK-
L0415	b4HB3MA Co8-HAP-Ft					Lafmid BA
L0438	normalized infant brain cDNA	total brain	brain			lafmid BA
L0439	Soares infant brain 1NIB		whole brain			Lafmid BA
L0455	Human retina cDNA randomly primed sublibrary	retina	eye			lambda gt10
L0456	Human retina cDNA Tsp509I-cleaved sublibrary	retina	eye			lambda gt10
L0471	Human fetal heart, Lambda ZAP Express					Lambda ZAP Express
L0475	KG1-a Lambda Zap Express cDNA library			KG1-a		Lambda Zap Express (Stratagene)
L0480	Stratagene cat#937212 (1992)					Lambda ZAP, pBluescript SK(-)
L0483	Human pancreatic islet					Lambda ZAPII
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215.	skeletal muscle	leg muscle			Lambda ZAPII
L0493	NCI_CGAP_Ov26	papillary serous carcinoma	ovary			pAMP1
L0515	NCI_CGAP_Ov32	papillary serous carcinoma	ovary			pAMP1
L0517	NCI_CGAP_Pr1					pAMP10
L0518	NCI_CGAP_Pr2					pAMP10
L0519	NCI_CGAP_Pr3					pAMP10
L0520	NCI_CGAP_Alve1	alveolar rhabdomyosarcoma				pAMP10
L0521	NCI_CGAP_Ew1	Ewing's sarcoma				pAMP10
L0523	NCI_CGAP_Lip2	liposarcoma				pAMP10
L0526	NCI_CGAP_Pr12	metastatic prostate bone lesion				pAMP10
L0529	NCI_CGAP_Pr6	prostate				pAMP10

L0564	Jia bone marrow stroma	bone marrow stroma				pBluescript
L0565	Normal Human Trabecular Bone Cells	Bone	Hip			pBluescript
L0581	Stratagene liver (#937224)		liver			pBluescript SK
L0584	Stratagene cDNA library Human heart, cat#936208					pBluescript SK(+)
L0588	Stratagene endothelial cell 937223					pBluescript SK-
L0589	Stratagene fetal retina 937202					pBluescript SK-
L0590	Stratagene fibroblast (#937212)					pBluescript SK-
L0591	Stratagene HeLa cell s3 937216					pBluescript SK-
L0592	Stratagene hNT neuron (#937233)					pBluescript SK-
L0593	Stratagene neuroepithelium (#937231)					pBluescript SK-
L0596	Stratagene colon (#937204)		colon			pBluescript SK-
L0599	Stratagene lung (#937210)		lung			pBluescript SK-
L0600	Weizmann Olfactory Epithelium	olfactory epithelium	nose			pBluescript SK-
L0601	Stratagene pancreas (#937208)		pancreas			pBluescript SK-
L0602	Pancreatic Islet	pancreatic islet	pancreas			pBluescript SK-
L0603	Stratagene placenta (#937225)		placenta			pBluescript SK-
L0604	Stratagene muscle 937209	muscle	skeletal muscle			pBluescript SK-
L0605	Stratagene fetal spleen (#937205)	fetal spleen	spleen			pBluescript SK-
L0606	NCI_CGAP_Lym5	follicular lymphoma	lymph node			pBluescript SK-
L0607	NCI_CGAP_Lym6	mantle cell lymphoma	lymph node			pBluescript SK-
L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69		pBluescript SK-
L0622	HM1					pcDNAII (Invitrogen)
L0623	HM3	pectoral muscle (after mastectomy)				pcDNAII (Invitrogen)
L0629	NCI_CGAP_Mel3	metastatic melanoma to bowel	bowel (skin primary)			pCMV-SPORT4
L0631	NCI_CGAP_Br7		breast			pCMV-SPORT4
L0636	NCI_CGAP_Pit1	four pooled pituitary adenomas	brain			pCMV-SPORT6
L0637	NCI_CGAP_Bm53	three pooled meningiomas	brain			pCMV-SPORT6
L0638	NCI_CGAP_Bm35	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0639	NCI_CGAP_Bm52	tumor, 5 pooled (see description)	brain			pCMV-SPORT6
L0640	NCI_CGAP_Br18	four pooled high-grade tumors, including two prima	breast			pCMV-SPORT6
L0641	NCI_CGAP_Co17	juvenile granulosa	colon			pCMV-

		tumor				SPORT6
L0643	NCI_CGAP_Co19	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0645	NCI_CGAP_Co21	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0646	NCI_CGAP_Co14	moderately differentiated adenocarcinoma	colon			pCMV-SPORT6
L0647	NCI_CGAP_Sar4	five pooled sarcomas, including myxoid liposarcoma	connective tissue			pCMV-SPORT6
L0648	NCI_CGAP_Eso2	squamous cell carcinoma	esophagus			pCMV-SPORT6
L0649	NCI_CGAP_GU1	2 pooled high-grade transitional cell tumors	genitourinary tract			pCMV-SPORT6
L0653	NCI_CGAP_Lu28	two pooled squamous cell carcinomas	lung			pCMV-SPORT6
L0654	NCI_CGAP_Lu31		lung, cell line			pCMV-SPORT6
L0655	NCI_CGAP_Lym12	lymphoma, follicular mixed small and large cell	lymph node			pCMV-SPORT6
L0656	NCI_CGAP_Ov38	normal epithelium	ovary			pCMV-SPORT6
L0657	NCI_CGAP_Ov23	tumor, 5 pooled (see description)	ovary			pCMV-SPORT6
L0659	NCI_CGAP_Pan1	adenocarcinoma	pancreas			pCMV-SPORT6
L0661	NCI_CGAP_Mel15	malignant melanoma, metastatic to lymph node	skin			pCMV-SPORT6
L0662	NCI_CGAP_Gas4	poorly differentiated adenocarcinoma with signet r	stomach			pCMV-SPORT6
L0663	NCI_CGAP_Ut2	moderately-differentiated endometrial adenocarcinoma	uterus			pCMV-SPORT6
L0664	NCI_CGAP_Ut3	poorly-differentiated endometrial adenocarcinoma	uterus			pCMV-SPORT6
L0665	NCI_CGAP_Ut4	serous papillary carcinoma, high grade, 2 pooled t	uterus			pCMV-SPORT6
L0666	NCI_CGAP_Ut1	well-differentiated endometrial adenocarcinoma, 7	uterus			pCMV-SPORT6
L0667	NCI_CGAP_CML1	myeloid cells, 18 pooled CML cases, BCR/ABL rearra	whole blood			pCMV-SPORT6
L0717	Gessler Wilms tumor					pSPORT1
L0731	Soares_pregnant_uterus_NbHPU		uterus			pT7T3-Pac
L0740	Soares melanocyte 2NbHM	melanocyte				pT7T3D (Pharmacia) with a modified polylinker

L0742	Soares adult brain N2b5HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0743	Soares breast 2NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0744	Soares breast 3NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0745	Soares retina N2b4HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0746	Soares retina N2b5HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0747	Soares_fetal_heart_NbHH 19W		heart			pT7T3D (Pharmacia) with a modified polylinker
L0748	Soares fetal liver spleen 1NFLS		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0749	Soares_fetal_liver_spleen _1NFLS_S1		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0750	Soares_fetal_lung_NbHL1 9W		lung			pT7T3D (Pharmacia) with a modified polylinker
L0751	Soares ovary tumor NbHOT	ovarian tumor	ovary			pT7T3D (Pharmacia) with a modified polylinker
L0752	Soares_parathyroid_tumor _NbHPA	parathyroid tumor	parathyroid gland			pT7T3D (Pharmacia) with a modified polylinker
L0753	Soares_pineal_gland_N3H PG		pineal gland			pT7T3D (Pharmacia) with a modified polylinker
L0754	Soares placenta Nb2HP		placenta			pT7T3D (Pharmacia) with a modified

						polylinker
L0755	Soares_placenta_8to9weeks_2NbHP8to9W		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0756	Soares_multiple_sclerosis_2NbHMSP	multiple sclerosis lesions				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0757	Soares_senescent_fibroblasts_NbHSF	senescent fibroblast				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0758	Soares_testis_NHT					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0759	Soares_total_fetus_Nb2HF8_9w					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0761	NCI_CGAP_CLL1	B-cell, chronic lymphocytic leukemia				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0762	NCI_CGAP_Br1.1	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0763	NCI_CGAP_Br2	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0764	NCI_CGAP_Co3	colon				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0766	NCI_CGAP_GCB1	germinal center B cell				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0768	NCI_CGAP_GC4	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0769	NCI_CGAP_Brn25	anaplastic oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker

L0770	NCI_CGAP_Brn23	glioblastoma (pooled)	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0771	NCI_CGAP_Co8	adenocarcinoma	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0772	NCI_CGAP_Co10	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0773	NCI_CGAP_Co9	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0774	NCI_CGAP_Kid3		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0775	NCI_CGAP_Kid5	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0776	NCI_CGAP_Lu5	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0777	Soares_NhHMPu_S1	Pooled human melanocyte, fetal heart, and pregnant	mixed (see below)			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0779	Soares_NFL_T_GBC_S1		pooled			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0782	NCI_CGAP_Pr21	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0784	NCI_CGAP_Lei2	leiomyosarcoma	soft tissue			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0786	Soares_NbHFB		whole brain			pT7T3D-Pac (Pharmacia) with a modified

						polylinker
L0787	NCI_CGAP_Sub1					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0788	NCI_CGAP_Sub2					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0789	NCI_CGAP_Sub3					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0790	NCI_CGAP_Sub4					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0791	NCI_CGAP_Sub5					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0792	NCI_CGAP_Sub6					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0793	NCI_CGAP_Sub7					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0794	NCI_CGAP_GC6	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0796	NCI_CGAP_Brn50	medulloblastoma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0800	NCI_CGAP_Co16	colon tumor, RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0803	NCI_CGAP_Kid11		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0805	NCI_CGAP_Lu24	carcinoid	lung			pT7T3D-Pac (Pharmacia)

						with a modified polylinker
L0806	NCI_CGAP_Lu19	squamous cell carcinoma, poorly differentiated (4	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0807	NCI_CGAP_Ov18	fibrotheoma	ovary			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0809	NCI_CGAP_Pr28		prostate			pT7T3D-Pac (Pharmacia) with a modified polylinker
L2251	Human fetal lung	Fetal lung				

TABLE 5

OMIM Reference	Description
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No entry.

Polynucleotide and Polypeptide Variants

[86] The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:Y, the nucleotide sequence of SEQ ID NO:X encoding the polypeptide sequence as defined in column 7 of Table 1A, nucleotide sequences encoding the polypeptide as defined in column 7 of Table 1A, the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, the nucleotide sequence as defined in column 6 of Table 1B, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1B, the cDNA sequence contained in Clone ID NO:Z, and/or nucleotide sequences encoding the polypeptide encoded by the cDNA sequence contained in Clone ID NO:Z.

[87] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, the polypeptide sequence as defined in column 7 of Table 1A, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, a polypeptide sequence encoded by the nucleotide sequence as defined in column 6 of Table 1B, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA sequence contained in Clone ID NO:Z.

[88] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

[89] Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence

selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of Clone ID NO:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in Clone ID NO:Z which encodes the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA in Clone ID NO:Z which encodes a mature polypeptide; (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes a biologically active fragment of a polypeptide; (e) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes an antigenic fragment of a polypeptide; (f) a nucleotide sequence encoding a polypeptide comprising the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (g) a nucleotide sequence encoding a mature polypeptide of the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (h) a nucleotide sequence encoding a biologically active fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (i) a nucleotide sequence encoding an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (j) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above.

[90] The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), or (j) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in Clone ID NO:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z, the nucleotide coding sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded

by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in column 7 of Table 1A or the complementary strand thereto, nucleotide sequences encoding the polypeptide as defined in column 7 of Table 1A or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

[91] In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i), above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[92] In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (b) the amino acid sequence of a mature form of a polypeptide having the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (c) the amino acid sequence of a biologically active fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (d) the amino acid sequence of an antigenic fragment of a polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z.

[93] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in Clone ID NO:Z, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B, the amino acid sequence as defined in column 7 of Table 1A, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

[94] By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1A or 2 as the ORF (open reading frame), or any fragment specified as described herein.

[95] As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also

referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

[96] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[97] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject

sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[98] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[99] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., the amino acid sequence identified in column 6) or Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polynucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence of the polypeptide encoded by cDNA contained in Clone ID NO:Z, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both

amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[100] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[101] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity

calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[102] The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

[103] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985)). These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

[104] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. As an example, Ron et al. (*J. Biol. Chem.* 268: 2984-2988 (1993)) reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

[105] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem.* 268:22105-22111 (1993)) conducted extensive mutational

analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[106] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[107] Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptides of the invention. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

[108] The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., *Human Chromosomes: A Manual of Basic Techniques*, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA

expression in specific tissues (e.g., normal or diseased tissues); and (4) *in situ* hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal or diseased tissues).

[109] Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an anti-polypeptide of the invention antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

[110] The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

[111] For example, in one embodiment where one is assaying for the ability to bind or compete with a full-length polypeptide of the present invention for binding to an anti-polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, *in situ* immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[112] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., *Microbiol. Rev.* 59:94-123 (1995). In another embodiment, the ability of physiological correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

[113] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either *in vitro* or *in vivo*). Other methods will be known to the skilled artisan and are within the scope of the invention.

[114] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA contained in Clone ID NO:Z, the nucleic acid sequence referred to in Table 1A (SEQ ID NO:X), the nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[115] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1306-1310 (1990), wherein the

authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[116] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[117] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham and Wells, Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

[118] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), (iv) fusion of the polypeptide with

additional amino acids, such as, for example, an IgG Fc fusion region peptide, serum albumin (preferably human serum albumin) or a fragment thereof, or leader or secretory sequence, or a sequence facilitating purification, or (v) fusion of the polypeptide with another compound, such as albumin (including but not limited to recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[119] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

[120] A further embodiment of the invention relates to polypeptides which comprise the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, an amino acid sequence encoded by the complement of SEQ ID NO:X, and/or an amino acid sequence encoded by cDNA contained in Clone ID NO:Z which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

[121] In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein); (b) the amino acid sequence encoded by SEQ ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the

complement of SEQ ID NO:X or fragments thereof; (d) the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in Clone ID NO:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotide and Polypeptide Fragments

[122] The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEQ ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto.

[123] The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to

include 20 or more contiguous bases from the cDNA sequence contained in Clone ID NO:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

[124] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a

polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[125] Further representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in Clone ID NO:Z, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under

stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[126] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1B column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence delineated in column 6 of Table 1B. In further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[127] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1B, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode

these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[128] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[129] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[130] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[131] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X (e.g., as described herein) are directly

contiguous Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[132] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[133] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table 1B, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[134] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a portion of an amino acid sequence encoded by the cDNA contained in Clone ID NO:Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of cDNA and SEQ ID NO: Y. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130,

140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[135] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[136] Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

[137] The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, N-terminal

deletions may be described by the general formula $m-q$, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to $q-6$. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[138] The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, C-terminal deletions may be described by the general formula $1-n$, where n is any whole integer ranging from 6 to $q-1$, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[139] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues $m-n$ of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), the cDNA contained in Clone ID NO:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[140] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened muetin to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such

immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[141] The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[142] Any polypeptide sequence encoded by, for example, the polynucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in Clone ID NO:Z, or the polynucleotide sequence as defined in column 6 of Table 1B, may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2) or the cDNA contained in Clone ID NO:Z may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

[143] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha- and beta-amphipathic regions; Karplus-Schulz flexible regions; Emini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

[144] Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing

four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[145] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described herein.

[146] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[147] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[148] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEQ ID NO:Y; a polypeptide sequence encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereto; the polypeptide sequence encoded by the cDNA contained in Clone ID NO:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEQ ID NO:X as defined in

columns 8 and 9 of Table 2, or the cDNA sequence contained in Clone ID NO:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined *supra*.

[149] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[150] Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

[151] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic

epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[152] Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y specified in column 7 of Table 1A. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index which is included in the DNASTar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y shown in column 7 of Table 1A, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y. The flanking sequence may, however, be sequences from a heterologous polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO:Y shown in column 7 of Table 1A.

[153] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10

amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[154] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[155] As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a

preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[156] Such fusion proteins as those described above may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972-897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain

for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni²⁺ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Fusion Proteins

[157] Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[158] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[159] In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

[160] Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

[161] As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with

heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).

[162] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a polypeptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)).

[163] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to

modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., *Curr. Opin. Biotechnol.* 8:724-33 (1997); Harayama, *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, et al., *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo and Blasco, *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[164] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Recombinant and Synthetic Production of Polypeptides of the Invention

[165] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[166] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

[167] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli* lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[168] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418, glutamine synthase, or neomycin resistance for eukaryotic cell culture, and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[169] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[170] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell

lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

[171] The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

[172] Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis *et al.*, *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[173] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., the coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al.*, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra *et al.*, *Nature* 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[174] Polypeptides of the invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

[175] Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this

prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[176] In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O₂. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O₂. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[177] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[178] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[179] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[180] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[181] In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, *Proteins: Structures and Molecular Principles*, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer amino acids such as β -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids,

and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[182] The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH_4 ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[183] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[184] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine (^{121}I , ^{123}I , ^{125}I , ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{111}In , ^{112}In , $^{113\text{m}}\text{In}$, $^{115\text{m}}\text{In}$), technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , and ^{97}Ru .

[185] In specific embodiments, a polypeptide of the present invention or fragment or variant thereof is attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, ^{177}Lu , ^{90}Y , ^{166}Ho , and ^{153}Sm , to polypeptides. In a preferred

embodiment, the radiometal ion associated with the macrocyclic chelators is ^{111}In . In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is ^{90}Y . In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane- $\text{N},\text{N}',\text{N}'',\text{N}'''$ -tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., *Clin Cancer Res.* 4(10):2483-90 (1998); Peterson et al., *Bioconjug. Chem.* 10(4):553-7 (1999); and Zimmerman et al, *Nucl. Med. Biol.* 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

[186] As mentioned, the proteins of the invention may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Polypeptides of the invention may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, *PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES*, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); *POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS*, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., *Meth. Enzymol.* 182:626-646 (1990); Rattan et al., *Ann. N.Y. Acad. Sci.* 663:48-62 (1992)).

[187] Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[188] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[189] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconj. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[190] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF),

herein incorporated by reference; see also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[191] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[192] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[193] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992); Francis et al., *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[194] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($\text{ClSO}_2\text{CH}_2\text{CF}_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

[195] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[196] The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-

15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

[197] The polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[198] The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

[199] Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer refers to a multimer containing only polypeptides corresponding to a protein of the invention (e.g., the amino acid sequence of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or an amino acid sequence encoded by cDNA contained in Clone ID NO:Z (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein)). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing two polypeptides having identical or different

amino acid sequences) or a homotrimer (e.g., containing three polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[200] As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

[201] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in Clone ID NO:Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent

associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[202] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

[203] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

[204] In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, proteins of the invention

are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[205] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[206] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or

hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

[207] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEQ ID NO:Y or a polypeptide encoded by the cDNA contained in Clone ID No:Z, and/or an epitope, of the present invention) as determined by immunoassays well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

[208] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')₂, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the

antibodies are human, murine (e.g., mouse and rat), donkey, sheep rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[209] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[210] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include the predicted epitopes shown in column 7 of Table 1A, as well as polynucleotides that encode these epitopes. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

[211] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the

corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

[212] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[213] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its

substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[214] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Ljautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol. Chem.* 272(17):11295-11301 (1997); Taryman et al., *Neuron* 14(4):755-762 (1995); Muller et al., *Structure* 6(9):1153-1167 (1998); Bartunek et al., *Cytokine* 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[215] Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., *Antibodies: A*

Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

[216] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387; the disclosures of which are incorporated herein by reference in their entireties.

[217] The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[218] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[219] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[220] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[221] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[222] Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for

example, the protocol outlined in Chapter 7.22 of *Current Protocols in Immunology*, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

[223] In general, the sample containing human B cells is inoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g., SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

[224] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')₂ fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). F(ab')₂ fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

[225] For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[226] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[227] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999 (1993); and

Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[228] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO

96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[229] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181; and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[230] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., *Bio/technology* 12:899-903 (1988)).

[231] Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, *FASEB J.* 7(5):437-444; (1989) and Nissinoff, J. *Immunol.* 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies which bind to and enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization, binding and/or signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

[232] Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., *Hum. Gene Ther.* 5:595-601 (1994); Marasco, W.A., *Gene Ther.* 4:11-15 (1997); Rondon and Marasco, *Annu. Rev. Microbiol.* 51:257-283 (1997); Proba et al., *J. Mol. Biol.* 275:245-253 (1998); Cohen et al., *Oncogene* 17:2445-2456 (1998); Ohage and Steipe, *J. Mol. Biol.* 291:1119-1128 (1999); Ohage et al., *J. Mol. Biol.* 291:1129-1134 (1999); Wirtz and Steipe, *Protein Sci.* 8:2245-2250 (1999); Zhu et al., *J. Immunol. Methods* 231:207-222 (1999); and references cited therein.

Polynucleotides Encoding Antibodies

[233] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y, to a polypeptide encoded by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

[234] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[235] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[236] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g.,

recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[237] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[238] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from

different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[239] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

[240] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

[241] Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors

may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[242] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[243] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster

ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

[244] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[245] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[246] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in

infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[247] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[248] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell

lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

[249] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., *Cell* 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, *Proc. Natl. Acad. Sci. USA* 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., *Cell* 22:817 (1980)) genes can be employed in tk-, hgp^{rt}- or ap^{rt}- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., *Natl. Acad. Sci. USA* 77:357 (1980); O'Hare et al., *Proc. Natl. Acad. Sci. USA* 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, *Proc. Natl. Acad. Sci. USA* 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 *Clinical Pharmacy* 12:488-505; Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, 1993, *TIB TECH* 11(5):155-215 (1993)); and hyg^{ro}, which confers resistance to hygromycin (Santerre et al., *Gene* 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin et al., *J. Mol. Biol.* 150:1 (1981), which are incorporated by reference herein in their entireties.

[250] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, *The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning*, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., *Mol. Cell. Biol.* 3:257 (1983)).

[251] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entireties by reference herein.

[252] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, *Nature* 322:52 (1986); Kohler, *Proc. Natl. Acad. Sci. USA* 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[253] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous

polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[254] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either *in vitro* or *in vivo*, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., *Immunol. Lett.* 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., *PNAS* 89:1428-1432 (1992); Fell et al., *J. Immunol.* 146:2446-2452 (1991), which are incorporated by reference in their entireties.

[255] The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., *Proc. Natl. Acad. Sci. USA* 88:10535-10539 (1991); Zheng et al., *J.*

Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

[256] As discussed, *supra*, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; and Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., J. Biochem. 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).

[257] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[258] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{111}In or ^{99}Tc .

[259] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol,

streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[260] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- α , TNF- β , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[261] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[262] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic

Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

[263] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[264] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

[265] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the gene of the present invention may be useful as cell-specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

[266] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

[267] The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich"

immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[268] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds., (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

[269] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ³²P or ¹²⁵I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the

presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

[270] ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

[271] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

[272] Antibodies of the invention may be characterized using immunocytochemistry methods on cells (e.g., mammalian cells, such as CHO cells) transfected with a vector enabling the expression of an antigen or with vector alone using techniques commonly

known in the art. Antibodies that bind antigen transfected cells, but not vector-only transfected cells, are antigen specific.

Therapeutic Uses

[273] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[274] In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more diseases, disorders, or conditions, including but not limited to: neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, and/or as described elsewhere herein. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a polypeptide of the invention (such as, for example, a predicted linear epitope shown in column 7 of Table 1A; or a conformational epitope, including fragments, analogs and derivatives thereof as described

herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[275] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[276] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[277] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[278] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present

invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

[279] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[280] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[281] For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

[282] In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which

the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[283] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

[284] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

[285] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

[286] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[287] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

[288] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those

cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[289] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[290] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[291] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[292] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[293] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used.

Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[294] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Activity

[295] The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[296] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[297] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[298] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[299] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[300] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler

(eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

[301] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

[302] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[303] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[304] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in

animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[305] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the

composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[306] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[307] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[308] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

[309] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

[310] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

[311] The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[312] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium

(⁹⁹Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[313] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[314] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer; S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[315] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[316] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[317] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[318] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

[319] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[320] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or

cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[321] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[322] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[323] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[324] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin-coated plates can be used in conjunction with biotinylated antigen(s).

[325] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

[326] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[327] The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1A, column 9 provides the chromosome location of some of the polynucleotides of the invention.

[328] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

[329] Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

[330] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[331] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[332] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1A and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

[333] The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

[334] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian

Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library)). Column 10 of Table 1A provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 9 of Table 1A, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[335] Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

[336] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assays", and "Methods for Detecting Diseases").

[337] Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

[338] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31' mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[339] Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[340] By "measuring the expression level of polynucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[341] By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, vaginal pool, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue

biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[342] The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the invention attached may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, digestive disorders, metabolic disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced *supra* are hereby incorporated by reference in their entirety herein.

[343] The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., Science 254, 1497 (1991); and Egholm et al., Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA

hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T_{sub.m}) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[344] The compounds of the present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[345] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., *supra*)

[346] For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International

Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment, prevention, and/or prognosis of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

[347] In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

[348] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present

invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy Methods", and Examples 16, 17 and 18).

[349] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[350] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

[351] Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992)). Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to

the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

[352] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention, specific to tissues, including but not limited to those shown in Table 1A. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination. Additional non-limiting examples of such uses are further described herein.

[353] The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, those disclosed in column 8 of Table 1A, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

[354] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[355] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for

attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

[356] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[357] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[358] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[359] In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

[360] A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$, (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F , ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[361] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[362] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[363] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that

under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi , or other radioisotopes such as, for example, ^{103}Pd , ^{133}Xe , ^{131}I , ^{68}Ge , ^{57}Co , ^{65}Zn , ^{85}Sr , ^{32}P , ^{35}S , ^{90}Y , ^{153}Sm , ^{153}Gd , ^{169}Yb , ^{51}Cr , ^{54}Mn , ^{75}Se , ^{113}Sn , $^{90}\text{Yttrium}$, ^{117}Tin , $^{186}\text{Rhenium}$, $^{166}\text{Holmium}$, and $^{188}\text{Rhenium}$; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{90}Y . In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{111}In . In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{131}I .

[364] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[365] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a

disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[366] Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[367] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[368] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

Diagnostic Assays

[369] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those described herein under the section heading "Biological Activities".

[370] For a number of disorders, substantially altered (increased or decreased) levels of gene expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, that is, the expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves measuring the expression level of the gene encoding the polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a standard gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue.

[371] The present invention is also useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[372] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 8 (Tissue Distribution Library Code).

[373] By "assaying the expression level of the gene encoding the polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample

obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[374] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing polypeptides of the invention (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a polypeptide or mRNA. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[375] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, *Anal. Biochem.* 162:156-159 (1987). Levels of mRNA encoding the polypeptides of the invention are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[376] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of polypeptides of the invention, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of polypeptides of the invention compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying polypeptide levels in a biological sample can occur using any art-known method.

[377] Assaying polypeptide levels in a biological sample can occur using antibody-based techniques. For example, polypeptide expression in tissues can be studied

with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as glucose oxidase, and radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium ($^{99\text{m}}\text{Tc}$), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[378] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the gene of interest (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the gene.

[379] For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[380] In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the polypeptides of the invention (shown in column 7 of Table 1A) may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[381] In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a polypeptide of the invention may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence

techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[382] The antibodies (or fragments thereof), and/or polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or polypeptide of the present invention. The antibody (or fragment thereof) or polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the gene product, or conserved variants or peptide fragments, or polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[383] Immunoassays and non-immunoassays for gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[384] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled antibody or detectable polypeptide of the invention. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[385] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses,

polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[386] The binding activity of a given lot of antibody or antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[387] In addition to assaying polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, polypeptides and/or antibodies of the invention are used to image diseased cells, such as neoplasms. In another embodiment, polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of an mRNA) and/or antibodies (e.g., antibodies directed to any one or a combination of the epitopes of a polypeptide of the invention, antibodies directed to a conformational epitope of a polypeptide of the invention, or antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells.

[388] Antibody labels or markers for *in vivo* imaging of polypeptides of the invention include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or

otherwise known in the art. For example methods for producing chimeric antibodies are known in the art. See, for review, Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., *Nature* 312:643 (1984); Neuberger et al., *Nature* 314:268 (1985).

[389] Additionally, any polypeptides of the invention whose presence can be detected, can be administered. For example, polypeptides of the invention labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further, such polypeptides can be utilized for *in vitro* diagnostic procedures.

[390] A polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the antigenic protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[391] With respect to antibodies, one of the ways in which an antibody of the present invention can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL.; Ishikawa, E. et al., (eds.), 1981,

Enzyme Immunoassay, Kigaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[392] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect polypeptides through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[393] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[394] The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[395] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by

detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, therromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[396] Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Methods for Detecting Diseases

[397] In general, a disease may be detected in a patient based on the presence of one or more proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a disease or disorder, including cancer and/or as described elsewhere herein. In addition, such proteins may be useful for the detection of other diseases and cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding polypeptides of the invention, which is also indicative of the presence or absence of a disease or disorder, including cancer. In general, polypeptides of the invention should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

[398] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra*. In general, the presence or absence of a disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

[399] In a preferred embodiment, the assay involves the use of a binding agent(s) immobilized on a solid support to bind to and remove the polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection

reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include polypeptides of the invention and portions thereof, or antibodies, to which the binding agent binds, as described above.

[400] The solid support may be any material known to those of skill in the art to which polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[401] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both

the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

Gene Therapy Methods

[402] Also encompassed by the invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[403] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[404] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like).

The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[405] In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[406] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[407] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoA1 promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[408] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[409] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[410] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[411] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[412] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[413] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[414] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

[415] Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[416] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[417] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can

also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[418] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[419] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology* (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+} -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* 17:77 (1979)); ether injection (Deamer, D. and Bangham, A., *Biochim. Biophys. Acta* 443:629 (1976); Ostro et al., *Biochem. Biophys.*

Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

[420] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[421] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

[422] In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[423] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and

CaPO₄ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[424] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a polypeptide of the present invention.

[425] In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al. *Am. Rev. Respir. Dis.* 109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) *Science* 252:431-434; Rosenfeld et al., (1992) *Cell* 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) *Proc. Natl. Acad. Sci. USA* 76:6606).

[426] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, *Curr. Opin. Genet. Devel.* 3:499-503 (1993); Rosenfeld et al., *Cell* 68:143-155 (1992); Engelhardt et al., *Human Genet. Ther.* 4:759-769 (1993); Yang et al., *Nature Genet.* 7:362-369 (1994); Wilson et al., *Nature* 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[427] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting

cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[428] In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[429] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

[430] Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), which are herein incorporated by reference. This method involves the

activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[431] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[432] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[433] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[434] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[435] The polynucleotide encoding a polypeptide of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be

transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[436] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[437] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[438] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[439] Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising polypeptides of the invention for targeting the vehicle to a particular site.

[440] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA

189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[441] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[442] Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

Biological Activities

[443] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

[444] Blood and blood-forming organ associated proteins are believed to be involved in biological activities associated with coagulation, hematopoiesis, angiogenesis, cardiovascular functions, immune functions, metabolism, and endocrine functions. Accordingly, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, detection and/or treatment of diseases and/or disorders associated with aberrant blood-function or formation.

[445] In preferred embodiments, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders relating to blood and blood formation (e.g., blood coagulation disorders (e.g., hemophilia); blood clotting disorders (e.g., thromboembolism, and pulmonary embolism); fibrinolysis disorders; complement activation disorders (e.g., complement component deficiencies); hematopoietic disorders (e.g., X-linked agammaglobulinemia, anemia); immune system disorders (e.g., autoimmunity and immunodeficiencies); and/or as described under "Immune Activity", "Cardiovascular Disorders", and "Blood Disorders" below) and neoplastic disorders (e.g., cell migration, prohormone activation, extracellular matrix turnover, and/or as described under "Immune Activity" and "Hyperproliferative Disorders" below).

[446] In another embodiment, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used to treat and/or prevent unwanted side effects and/or complications of other therapeutic treatments (e.g. kidney dialysis, chemotherapy, radiation therapy, and organ/tissue transplant).

[447] Additionally, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, prognosis, prevention, and/or treatment of infectious or parasitic diseases and/or of conditions that are associated with infectious or parasitic diseases (e.g., AIDS, viral hepatitis, and/or as described in the section entitled "Infectious Diseases").

[448] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 8 (Tissue Distribution Library Code).

[449] Thus, polynucleotides, translation products and antibodies of the invention are useful in the diagnosis, prognosis, prevention, and/or treatment of diseases or disorders associated with activities that include, but are not limited to, blood coagulation, fibrinolysis,

complement activation, regulation of the immune system and of immune system cells, inflammation, cell migration and prohormone activation.

[450] More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, detection and/or treatment of diseases and/or disorders associated with the following systems.

Blood-Related Disorders

[451] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[452] In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[453] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 8 (Tissue Distribution Library Code).

[454] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[455] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

[456] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary sideroblastic anemia, idiopathic acquired sideroblastic anemia, red cell

aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune hemolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyl dopa, dapsone, and/or sulfadiazine. Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[457] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

[458] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thrombasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophilia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorrhagic Telangiectasia, also

known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[459] The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[460] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[461] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leukocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

[462] Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[463] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndrome, severe combined immunodeficiency, ataxia telangiectasia).

[464] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[465] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing,

preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[466] In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphoblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[467] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[468] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myeloid metaplasia, thrombocythemia, (including both primary and secondary thrombocythemia) and chronic myelocytic leukemia.

[469] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

[470] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

[471] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the

number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[472] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

[473] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

Immune Activity

[474] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

[475] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 8 (Tissue Distribution Library Code).

[476] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[477] In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

[478] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[479] In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

[480] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic aplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[481] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[482] In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[483] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response,

particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[484] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henoch-Schoenlein purpura), autoimmune cytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[485] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[486] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g.,

by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[487] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomyopathy (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[488] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[489] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[490] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[491] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention

[492] In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

[493] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[494] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[495] Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose IgE-mediated

allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

[496] Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

[497] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not

limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chondritis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[498] In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[499] In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[500] Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by

increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[501] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

[502] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[503] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein

or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[504] In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

[505] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[506] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

[507] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

[508] In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-

human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

[509] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

[510] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

[511] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[512] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

[513] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

[514] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

[515] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

[516] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation,

prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[517] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[518] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[519] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[520] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[521] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[522] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

[523] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

[524] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

[525] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[526] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[527] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

[528] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[529] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

[530] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

[531] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

[532] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

[533] The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

[534] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

[535] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

[536] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

[537] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

[538] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

[539] In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or

polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[540] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[541] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[542] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[543] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[544] In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

[545] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention

include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

[546] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention.

Hyperproliferative Disorders

[547] In certain embodiments, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

[548] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

[549] Examples of hyperproliferative disorders that can be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[550] Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragenital Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye

Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[551] In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[552] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

[553] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[554] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriadigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, facioidigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertbral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[555] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[556] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to